



University of
Nottingham
UK | CHINA | MALAYSIA

Realising the potential of wearable magnetoencephalography

Thesis submitted to the University of Nottingham for the
degree of Doctor of Philosophy

April 2025

Gonzalo Reina Rivero

1420757

Supervisors: Matthew J. Brookes, Niall Holmes
and Elena Boto

School of Physics and Astronomy
University of Nottingham

Contents

Abstract	ix
Acknowledgments	xi
Chapter 1 Introduction	14
1.1 Thesis aims	18
1.2 Thesis outline	19
Chapter 2 Magnetoencephalography	23
2.1 The source of the MEG signal	23
2.1.1 Neurons and action potentials	23
2.1.2 Beyond the action potential	27
2.1.3 Local field potentials	30
2.1.4 Measurable effects	32
2.1.5 Spontaneous activity	32
2.1.6 Evoked responses	34
2.1.7 Induced responses	35
2.1.8 Functional connectivity	36
2.2 Measuring brain signals: MEG	37
2.2.1 Superconductivity	37
2.2.2 Josephson junctions	39
2.2.3 The DC SQUID	41
2.2.4 Noise reduction	44
2.2.5 Available SQUID-MEG systems	48
2.2.6 Limitations	49
Chapter 3 Optically pumped magnetometers	51
3.1 Emerging technologies	51

3.1.1 High Temperature SQUIDs	51
3.1.2 Hybrid SQUIDs	52
3.1.3 Nitrogen vacancy centre magnetometry	53
3.1.4 Tunnel magneto-resistive sensors	53
3.2 OPMs: An introduction	54
3.3 The atomic energy level structure	54
3.4 Fine structure	55
3.5 Hyperfine structure	58
3.6 Zeeman splitting	58
3.7 Optical pumping	61
3.8 Spin polarisation and magnetic field interaction	64
3.9 Optical detection	66
3.10 Spin exchange relaxation-free regime	68
3.11 Signal equations	71
3.12 Sensor bandwidth	75
3.13 Cross-Axis projection errors	75
3.14 Alternative approaches	77
3.15 Commercially available sensors	78
3.16 The QuSpin triaxial OPM	78
3.17 Field-zero and calibration	80
3.18 OPM array for MEG	82
Chapter 4 Signal processing in MEG	85
4.1 Filtering and artifact removal	85
4.2 Homogeneous field correction	86
4.3 The inverse problem	87
4.4 Forward model	88

4.5 Single sphere model	90
4.6 Single shell model	93
4.7 Alternative forward models	97
4.8 Beamforming	98
4.9 Other approaches	101
4.10 Source space analysis	101
4.10.1 Source signal envelope	102
4.10.2 Source localisation	102
4.10.3 Brain parcellation	104
4.10.4 Signal leakage correction	105
4.11 Bursting	106
4.11.1 Conventional burst analysis	106
4.11.2 Hidden Markov Models	106
4.11.3 Markov chains	107
4.11.4 Hidden states	108
4.11.5 Model inference	110
4.11.6 The observation model	113
Chapter 5 Magnetic shielding	114
5.1 Introduction	114
5.2 Passive shielding	115
5.2.1 Magnetically shielded rooms	115
5.2.2 Flux shunting	117
5.2.3 Eddy current shielding	118
5.2.4 Spherical shield	120
5.2.5 Demagnetisation	122
5.3 Active shielding	123

5.3.1 Coil systems	123
5.3.2 Bi-planar coils for OPM-MEG	126
Chapter 6 The role of beta bursts in top-down inhibition of somatosensory cortex: an OPM-MEG study	135
6.1 Abstract	135
6.2 Introduction	135
6.3 Methods	137
6.3.1 Tactile attention paradigm	137
6.3.2 OPM-MEG system overview	139
6.3.3 Background magnetic field control	140
6.3.4 Co-registration	141
6.3.5 Data Pre-processing	141
6.3.6 Source space analysis	142
6.3.7 Statistical analyses	144
6.4 Results	145
6.4.1 Beta band amplitude modulates with attention	146
6.4.2 Pan-spectral burst probability modulates with attention	149
6.5 Discussion	153
6.6 Conclusion	155
Chapter 7 Enabling ambulatory movement in wearable magnetoencephalography with matrix coil active magnetic shielding	156
7.1 Abstract	156
7.2 Introduction	156
7.3 Theory	158
7.4 Methods	160
7.4.1 Coil design	160
7.4.2 Driving electronics	160

7.4.3 OPMs and helmet	162
7.4.4 Optical tracking	163
7.4.5 Implementing the nulling	163
7.5 Results	167
7.5.1 Compensating field drifts measured by a stationary array	167
7.5.2 Compensating artefacts on a moving array	170
7.5.3 Preventing motion-induced sensor gain changes: phantom study	172
7.5.4 Effects of sensor gain changes	173
7.5.5 Effects on source reconstruction	177
7.6 MEG Demonstration	182
7.6.1 Sensor level and movement analysis	182
7.6.2 Source reconstruction	183
7.7 Discussion	188
Chapter 8 Determining sensor geometry and gain in a wearable MEG system	190
8.1 Abstract	190
8.2 Introduction	190
8.3 Methods	192
8.3.1 OPM-MEG system	192
8.3.2 Calibration with HALO	194
8.3.3 Calibration with matrix coils	196
8.3.4 Characterisation of the MC system	196
8.3.5 OPM Calibration procedure	201
8.3.6 Validation experiments	202
8.3.7 Human experiments: data acquisition	204
8.3.8 Data analysis	206

8.4 Results	208
8.4.1 Validation experiments	208
8.4.2 Human experiments	212
8.5 Discussion	219
8.6 Conclusion	222
Summary and outlook	224
Future work	225
Attentional modulation of the beta band	225
Active shielding	226
Sensor calibration and localisation	227
Final Remarks	228
Appendix I: Array formation variations	229
Bibliography	230

Abstract

Functional brain imaging has pushed the field of neuroscience towards unprecedented insights into neural dynamics. These advances have come in tandem with developments across many areas of physics, particularly quantum mechanics, which has been instrumental in the creation of quantum sensors that enable high-precision neuroimaging techniques like magnetoencephalography (MEG)—a non-invasive method for measuring the brain’s tiny magnetic fields ($\sim 10^{-12}$ to 10^{-15} Tesla) generated by neural activity. Conventional MEG systems rely on superconducting quantum interference devices (SQUIDS) cooled to near absolute zero temperatures using liquid helium, which necessitates a complex and expensive cryogenic infrastructure. These systems require subjects to remain almost completely immobile within a fixed, bulky scanner, severely restricting natural movement and potentially introducing artifacts related to head positioning. Sensor-to-scalp distance is also limited due to the insulation surrounding the sensors, substantially reducing the spatial resolution and signal-to-noise ratio of the recordings.

In recent years, the miniaturisation of optically pumped magnetometers has enabled the development of novel MEG systems, capable of overcoming the technical challenges of cryogenic MEG. Their ability to work at room temperature and small footprint, has made OPMs an ideal candidate for revolutionising MEG hardware. Recent work has not only demonstrated the feasibility of such systems but has also demonstrated some of the advantages of OPM-MEG. Notably, OPM-MEG has enabled neuroimaging of previously challenging populations, including infants and young children, by overcoming traditional constraints of movement and scanning environment. This is particularly important for advancing our understanding of neurodevelopmental disorders such as autism spectrum disorder (ASD), where early brain development and functional connectivity are key areas of investigation. It also offers brain imaging of participants in standing positions or during ambulatory movement. This capability is vital for investigating the neural basis of movement and its disruption in neurodegenerative conditions such as Parkinson’s disease or multiple sclerosis, where motor disfunction is a core symptom.

However, the versatility of OPMs does not come without constraints. Their dynamic range is limited by the inherent sensitivity of the optically pumped alkali vapor sensors, which can become saturated when exposed to magnetic fields exceeding their linear detection range. This strict requirement for a low-field environment means that, like SQUID-MEG, the system must be housed in a magnetically shielded room (MSR). Additionally, remnant fields inside the MSR must be cancelled out using active magnetic shielding from electromagnetic coil systems to obtain optimal OPM performance.

In this thesis, the sensitivity of OPM-MEG is demonstrated with a study on modulation of the beta band during visual attentional cues and tactile stimuli. Our results reveal significant differences in beta band power that highlight the ability of OPM-MEG to measure subtle neurophysiological effects. We observed distinct patterns of beta band (13-30 Hz) oscillatory activity in sensorimotor cortical regions, with notable decreases during visual cues indicating participants to ignore tactile stimuli on either one of their hands. Specifically, the OPM-MEG recordings demonstrated a temporally precise desynchronization of beta band activity immediately preceding and during sensory integration tasks, providing valuable insights into the neural mechanisms of attentional modulation. While previous OPM-MEG studies focused on robust, repeatable induced effects, this work shows that subtle attentional signals can not only be detected but also used to probe the individual trial dynamics underlying them.

Secondly, we developed a novel active shielding system for OPM-MEG. Borrowing ideas from magnetic resonance imaging, we designed and constructed a multi-coil system for active magnetic field cancellation. The design follows a matrix pattern that strategically distributes compensation currents to create a low magnetic field nulling environment. Unlike traditional passive shielding methods, our active shielding approach can dynamically respond to changes in the background, significantly reducing background noise and enhancing the signal-to-noise ratio of OPM-MEG recordings. The system was also employed to null the field during ambulatory movement of the participant, via optical tracking of the sensor positions. These results open up a wealth of possibilities for neuroimaging experiments, especially for studies on neurological conditions affecting motor function.

Lastly, we employed a similar matrix coil system to improve the calibration of the OPMs. Co-registration errors of the sensor array to the anatomy and gain changes can significantly impact the accuracy of source reconstruction in MEG. Here, we compared two different calibration methods: the matrix coil system and a head mounted system designed by the sensor manufacturer to generate dipole-like fields from a set of small coils. By producing known fields, we were able to calibrate and localise the sensors relative to each other. Our findings revealed that both calibration approaches improved the signal-to-noise of reconstructed sources, suggesting that the use of external known fields enables more accurate determination of sensor locations, orientations, and gain. This technical improvement represents a critical step towards enhancing the precision of OPM-MEG source reconstruction techniques. Together with the cognitive demonstrations presented, these technical advances mark an important step in the maturation of OPM-MEG as a neuroimaging tool, helping to pave the way toward realising its full potential in both research and clinical contexts.

Acknowledgments

While I am proud of the work presented in this thesis, it is the company I have had throughout this Ph.D. that I am most grateful for. The work enriched my mind, but the people enriched my life. At risk of this section turning into an endless list of names, I want to acknowledge everyone that has been a part of this journey.

I want to first thank my main supervisor, Professor Matt Brookes, your support and guidance have made this possible. Thanks for giving me the opportunity to do this Ph.D. and for showing me what it takes to do relevant research that has a good impact. I will take all that I have learned from you forward in my career, always striving to approach research with the same curiosity and dedication that you have. It takes a village to do this type of research, so I want to thank everyone in the MEG group at Nottingham, especially my second supervisor, Niall, whose work on shielding has made OPM-MEG possible. Your patience and support have been truly invaluable. From countless discussions to your willingness to help at every stage, I can only hope my work has been helpful in some way. I also hope we don't have to do an 8-hour calibration ever again (maybe your future Ph.D. students can deal with that). A massive thanks to Ryan and Lukas too, who were always happy to read through endless MATLAB scripts whenever I got stuck.

Thanks as well to everyone at Cerca and QuSpin— Dr. Elena Boto, Dr. Vishal Shah, Elliot, Frank, Jack, Holly (to name a few)—for your collaboration and support in making this research possible from the very beginning. I don't think any of us would be here without Boto et al., 2016 or Shah and Wakai, 2013. Double thanks to Holly and Ryan for their work on the OPM calibration experiments, I would not have a thesis without you, so I hope you'll drink as much as me after my viva (maybe not that much). Before you start thinking that I forgot—thank you, Molly, for being there from the very start. I'm truly grateful for your support, both inside and outside the lab. Ed, thank you as well. Though you're no longer part of the team, I'm glad our paths crossed, and I wish you the best of luck with your own Ph.D. You have both patiently listened to my many (probably too many) rants, and for that, I can't thank you enough. Just know that wherever I end up, you'll always have a friend in me (a friend with immaculate taste in film and music, it does not get better than that!).

I want to acknowledge everyone I met at the SPMIC, where this work took shape. A special thanks to Professor Richard Bowtell, whose contributions were instrumental in developing the shielding systems. I'm also grateful to everyone at the Barn, especially Natalie— I have always admired your work and dedication. Thanks to Dan Marsh, Tobi, Laura, Ross, Arthur, Max, Thea and many more for making the Barn such a nice place. Thanks again to Dan (Big

Dan) for your helpful expertise on FSL. Thanks to everyone for the countless pub trips and pub crawls (or, really, anything involving a pint). I'll miss our *definitely normal* conversations over *very healthy* amounts of drinks. A special shout-out to Ryan and Niall as well—thanks for all the fun (and free pints) during our many celebrations and conferences. I am now confident I can now keep up with you at the pub... although I'm not entirely sure I should be proud of that! Thanks as well Louise for keeping the SPMIC running and for all the laughs and the fun.

Quiero agradecer a mi familia. En primer lugar, a mis padres, por haberme apoyado incondicionalmente a lo largo de toda mi vida, de tantas maneras. Gracias por darme una vida llena de color, por estar siempre ahí, apoyando cada uno de mis intereses, ya sea en deportes, viajes o mi pasión por estudiar física. Gracias ama por cuidarme tanto y por preocuparte de que no me faltara nada, también llenarme la maleta de embutidos tantas veces. Gracias Aita por siempre haber alimentado mi interés por la ciencia, siempre comprándome libros y herramientas para que pudiera aprender, esta tesis os la dedico a vosotros. Gracias al resto de mi familia, sobre todo a mi prima Raquel y a mi tía Mari Paz, por siempre hacerme sentir tan bienvenido cada vez que he vuelto. Gracias tía por tantas comidas increíbles, si viviera en España creo que no cabría por las puertas.

Finalmente, ya que es lo único que vais a leer de esta tesis, quiero agradecer a todos mis amigos, me siento increíblemente afortunado de teneros en mi vida. Gracias a aquellos que me acompañan desde que tengo memoria, con quienes he compartido tantas risas y aventuras. Fer, Borja, Bladik, Gato, Beñat, Alecha, Naia, Asier, Javi, Pedro, Unai, Añua: sois una parte fundamental de quien soy, y sin vuestro apoyo y risas, este camino no habría sido posible. Gracias Bladik por acogerme innumerables veces y por haberme apoyado, espero poder ser un amigo igual de generoso que tú. Fer y a Borja, gracias por tantas risas y por traer tanta diversión a mi vida. A Bolero y los tertulianos del Berri, Xabio, Ainhoa, Arando, Iker, Josetxu y muchos más, gracias por hacerme sentir parte de Vitoria pese llevar tanto tiempo fuera, por las risas y por vuestra asombrosa habilidad cervecera. También gracias a Amaia por apoyarme tanto durante mi primer año. Thanks, Matt, for being up for all my crazy adventure ideas and for helping me take my mind off things. To everyone at Wallet Avenue, especially Liv, thanks for making the best part of two years so happy and fun. Thanks everyone—Chris, Gabby, Francesca—for all the parties, the laughs, and for listening to my many musings along the way.

Stefano, thanks for putting up with me as a flatmate—there was never a dull moment. I am glad you were there to share the Ph.D. struggle. Big thanks as well to Alberto and Alessandro for all the parties and fun moments. Dan (Welsh), I'll always appreciate our gym and swimming sessions—best of luck with your Ph.D.! Jess, thanks for pushing me to the finish line and listening to

my endless ramblings (I promise to stop eventually), you have been a great friend. I want to also say thanks to everyone from 262, especially Hugh and Alex, who have always checked in on me throughout this Ph.D. And lastly, Ander, I couldn't have done this without you. Thanks for being such a great friend and for putting a roof over my head (twice). I hope one day I can match your generosity. A todos, vuestra amistad ha sido un pilar constante, y siempre estaré agradecido por cada momento compartido.

Esta tesis se la dedico a mis abuelos y a mi prima Diana. Según Abuela y Amama yo era un santo, incapaz de error, así que el trabajo que hay en esta tesis aquí deber ser increíble.

Chapter 1 Introduction

The human brain is one of the most complex structures in the universe. It has evolved to manage a wide array of functions critical to human behaviour. These functions encompass sensory processing, motor control, homeostatic regulation, memory formation, and information processing. The brain's role in generating consciousness and facilitating higher-order cognitive processes, including emotional responses and social interactions, makes it a subject of significant scientific interest. Understanding the brain's operational mechanisms is essential for advancing our knowledge of cognition, behaviour, and neurological or psychiatric disorders. The field of neuroscience has made substantial progress in elucidating many of these mechanisms, establishing correlations between functionality and anatomical structures. This progress has been facilitated, in part, by the development of various non-invasive medical imaging techniques, which have emerged from advancements in physics and engineering

Neuroimaging techniques can be categorised into structural or functional methods. The first group includes Magnetic Resonance Imaging (MRI) (Lauterbur, 1973; Mansfield and Grannell, 1973) and x-ray computerised tomography (CT) (Hounsfield, 1973). These have been fundamental in the development of modern neuroscience and are utilised for their clinical applications in hospitals all around the world. They can produce in-vivo structural images of the brain with very high resolution (~ 1 mm) and excellent contrast between different tissue types. However, they only provide a piece of the puzzle. While a structural image may show no hint of disease, a person may still be affected by disorders that tamper with brain function rather than structure. In order to see the bigger picture, one must also consider brain activity, governed by the flow of electrical currents along neurons. Functional imaging techniques can record the measurable effects of brain activity in an indirect or direct manner. The nature of the measured signals leads to broad differences in system design, performance and clinical or research use cases. Examples of some the functional brain imaging systems available today are shown in Figure 1.1.

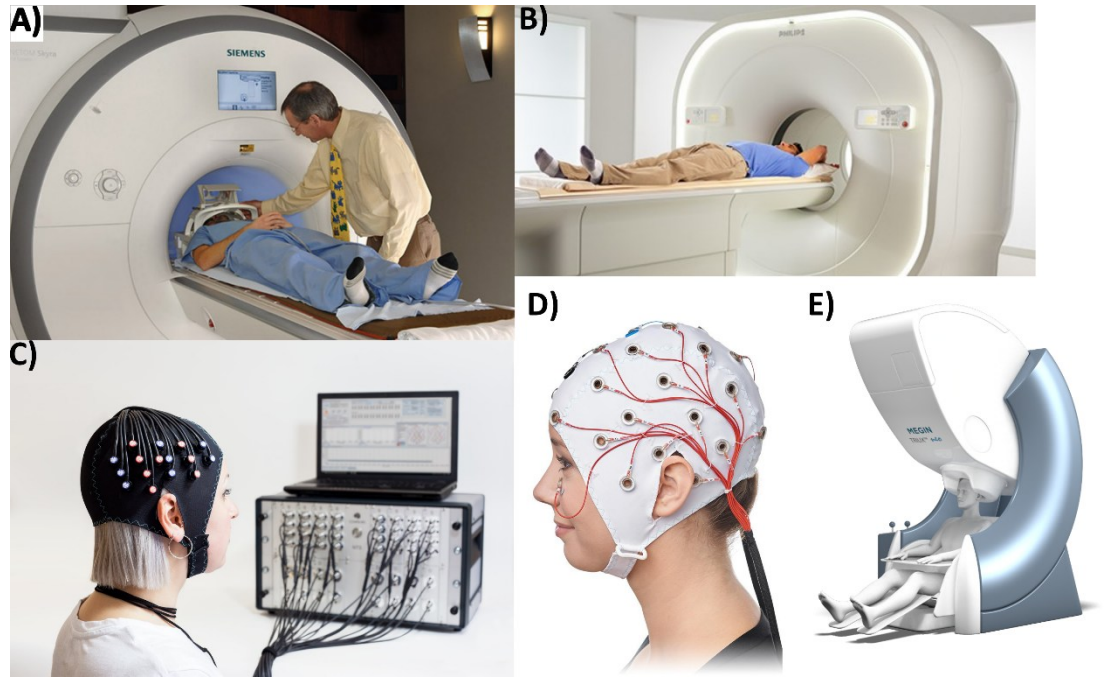


Figure 1.1 Modern brain imaging systems: *A) 3 Tesla Siemens Skyra MRI Scanner at the Hoglund Biomedical Imaging Centre, University of Kansas. B) Phillips Vereos PET-CT scanner. C) NTS fNIRS System from Gowerlabs. D) Brain Products EEG cap with electrode array. E) Megin MEG system.*

Starting with Functional Magnetic Resonance Imaging (fMRI), this technique utilises differences in blood oxygenation as an indirect measure of brain activity. Specifically, blood-oxygen level dependent (BOLD) contrast is a phenomenon that arises from oxygenated blood being delivered to active brain regions (Ogawa et al., 1990). Blood flow, volume and metabolic rate of oxygen can increase in regions where ensembles of neurons are firing repeatedly. This creates a difference in the magnetic properties of active brain regions compared to the surrounding areas. For example, in a resting brain region, the presence of paramagnetic deoxyhaemoglobin creates slight magnetic field inhomogeneities, which causes the T2* signal to decay faster. This technique detects this subtle increase in the T2* signal of active brain regions, which indicates a change in the blood oxygenation level and, by extension, neuronal activity. This method offers good spatial resolution; however, the nature of the BOLD response means fMRI operates on longer timescales. Blood oxygenation changes can occur in the order of seconds, lagging behind the underlying electrophysiological effects by which they are driven and perhaps more importantly, the behavioural effects that they underpin. The use of fMRI also introduces a number of constraints. As shown on Figure 1.1A, participants are required to stay still throughout the scan and lie inside the enclosed space of the magnet. This can make this approach ill-suited for certain cohorts, such as children, older people or participants with movement disorders. It also prevents some experiments being carried out, since participants are immobile, lying down with limited space and experiencing high levels of acoustic noise.

Positron emission tomography (PET) (Fox and Raichle, 1984; Ter-Pogossian et al., 1975) presents a different approach to obtain indirect measurements of brain activity. It can detect metabolic processes through the use of radioactive substances combined with compounds used by the human body. These are known as radiotracers; short-lived isotopes which undergo decay via positron-emission. Combined with biological molecules such as glucose, they accumulate in active brain regions. The annihilation event of the positron with a neighbouring electron emits two photons travelling in opposite directions, which can be detected by the scanner. This information is overlaid onto a structural image and can be used as a proxy to localise blood flow or compound absorption in the brain (Kinahan and Rogers, 1989). PET has similar drawbacks to fMRI, with a slightly lower spatial resolution ($\sim 4\text{-}6\text{ mm}$) and the need to keep participants still within the scanner (see Figure 1.1B). In addition to that, ionising radiation is required for this technique.

Lastly, we turn to functional near-infrared spectroscopy (fNIRS) (Jöbsis, 1977). Based on light absorption differences of near-infrared light by oxygenated or deoxygenated blood, it employs a set of light-emitting diodes that shine light in the near-infrared (NIR) range on to the scalp. The light can penetrate the brain thanks to the low absorption posed by the scalp and the skull. Scattered light rays are then recorded by neighbouring photodetectors. This approach is analogous to fMRI, capable of measuring differences in blood flow, volume and oxygenation. While it presents some advantages like much lower cost, portability and adaptability, allowing for movement of participants (Figure 1.1C). It has the drawback of lower spatial resolution ($\sim 1\text{-}3\text{ cm}$) and longer timescales ($\sim 100\text{ ms}$ to 1 s).

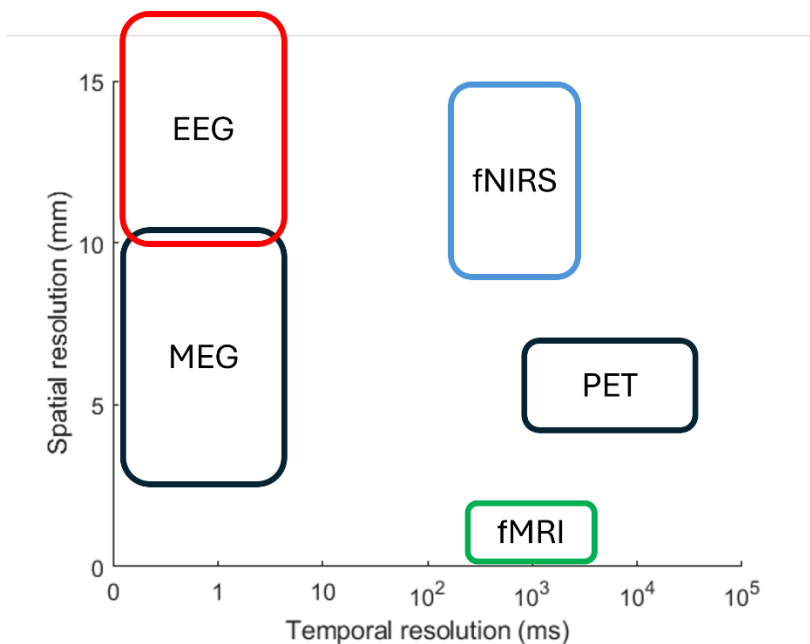


Figure 1.2: Spatial and temporal resolution of functional brain imaging techniques.

Direct functional neuroimaging techniques provide a more immediate metric of brain function without the need for intermediaries like blood flow. They can also overcome some hurdles posed by the methods mentioned above. Electroencephalography (EEG) is the most well known in this category. First developed in 1924 by Hans Berger, EEG is still in use in most hospitals and research centres around the world (Berger, 1929). As shown in Figure 1.1D, modern EEG employs a wearable cap holding an array of electrodes placed on the scalp, which are in electrical contact with the skin. These electrodes can then be used to measure changes in electrical potential across the scalp relative to a ground electrode. It offers millisecond temporal resolution. EEG systems are portable, can be easily adapted to different head sizes and are relatively inexpensive. This has made EEG the obvious choice for many clinical applications such as diagnosing epilepsy or sleep disorders. The electrical signals measured are nevertheless affected by the different conductivities of the brain, skull and scalp. This limits its spatial resolution to ~ 10 to 20 mm as electric field potentials from a small source pass through the different tissues and become spatially distorted. The requirement for electrical contact with the scalp also limits practicality and makes the setup time for EEG long.

Because the magnetic permeability of nearby tissues is nearly identical to that of free space, magnetic fields generated by neuronal currents experience less distortion than electrical potentials. MEG (Cohen, 1972) takes advantage of this by sampling magnetic fields outside the scalp with Super Conducting QUantum Interference Devices (SQUIDs). Doing so can provide better spatial resolution (~ 1 - 4 mm) than EEG while still being able to measure millisecond to millisecond changes in brain activity. SQUID sensors, however, require cryogenic temperatures to operate. This involves submerging them in liquid helium, which in turn adds a set of technical requirements such as a dewar container, thermal insulation, fixed sensor positioning and, in some cases, helium liquifying systems to capture the evaporating helium (e.g., Figure 1.1E). This makes SQUID-MEG systems quite large with a fixed size sensor array. Coverage will vary with participants with different head sizes, especially the younger ones with smaller heads. Movement is also constrained; participants are required to remain seated and cannot move their heads. Therefore, while having excellent spatial and temporal resolution, SQUID-MEG still presents significant challenges. Existing studies have looked at the clinical utility of both EEG and MEG, showing that MEG can indeed provide higher spatial resolution, which presents an advantage when evaluating patients with epilepsy (Tamilia et al., 2019). Concurrent EEG and MEG is already part of clinical practice guidelines for assessing epilepsy (Bagic et al., 2011).

In conclusion, the functional neuroimaging techniques discussed offer complementary windows into brain function, each with distinct advantages and limitations. Figure 1.2 illustrates this with a diagram outlining the spatial and temporal resolution of all these techniques. While direct techniques may offer a

more detailed insight into neuronal activity, the choice of imaging modality ultimately depends on the specific research or clinical objectives. For clinical applications, considerations such as cost-effectiveness, portability, and operational simplicity can sometimes favour techniques like EEG or fNIRS. In contrast, research applications may prioritize techniques that offer optimal spatiotemporal resolution, such as MEG or concurrent EEG-fMRI, despite their increased complexity and cost. Thus, rather than seeking a single perfect technique, the field benefits from this diverse toolkit, allowing researchers and clinicians to select methods that best align with their specific requirements and constraints.

1.1 Thesis aims

In recent years, the field of Magnetoencephalography has been revolutionised by the introduction of Optically Pumped Magnetometers (OPMs). The work presented here builds on this emerging technology, which has the potential to surmount many of the technical challenges presented by the neuroimaging techniques described in the previous section. OPMs offer several advantages over traditional SQUIDs, including operation at room temperature, reduced sensor-to-scalp distance, and the potential for more flexible and mobile MEG systems.

This thesis has two main objectives:

1. Demonstrating OPM-MEG Sensitivity in Cognitive Neuroscience:

We aim to showcase the sensitivity of OPM-MEG by measuring attentional modulation of beta oscillations in the somatosensory cortex during a spatially selective tactile attention task. While similar work on attentional modulation has been performed in the past with cryogenic MEG, suggesting beta band power is modulated during top-down inhibition, our study goes further. We demonstrate that OPM-MEG can not only measure such subtle effects but also probe the underlying bursting events that drive this modulation in the beta band. This enhanced sensitivity and spatial resolution of OPM-MEG opens new avenues for investigating fine-grained neural processes, potentially leading to more precise diagnoses and treatment monitoring in clinical settings.

2. Advancing OPM-MEG Technology through Improved Magnetic Shielding:

We present a novel calibration method for a matrix coil system designed for active magnetic shielding. This technological advancement aims to significantly improve OPM-MEG systems by providing a more flexible shielding solution and achieving a lower noise floor. Capable of nulling a volume of choice within the magnetically shielded room (MSR), this innovation broadens the possibilities for experimental paradigm design, including standing scans, ambulatory movement, and hyperscanning. By enhancing the versatility and performance of OPM-MEG systems, we pave the way for more naturalistic and ecologically valid neuroscientific experiments, as well as potential clinical applications that were previously challenging or impossible with traditional MEG systems. For example, these may include studies where patients with conditions affecting motor function (e.g., Parkinsons) are allowed to move, offering potential new insights into how exactly the brain operates in such cases.

By addressing these objectives, this thesis contributes to the ongoing transformation of MEG technology, bringing OPM-MEG closer to widespread clinical adoption. The improved sensitivity, spatial resolution, and flexibility offered by OPM-MEG, as demonstrated in this work, have the potential to revolutionize neuroimaging in both research and clinical contexts. These advancements may lead to earlier and more accurate diagnoses of neurological disorders, improved pre-surgical mapping, and enhanced monitoring of treatment efficacy, ultimately contributing to better patient outcomes in the field of neurology and neuropsychiatry.

1.2 Thesis outline

This thesis first covers the theoretical basis of MEG, outlining its underlying physics, sensor design for both SQUIDs and OPMs, and signal processing techniques. The experimental work that follows contributes significantly to pushing OPM-MEG technology closer to clinical applications, addressing key challenges and demonstrating its enhanced capabilities. The chapters are structured in the following manner:

- **Theory**
 - **Chapter 2 – Magnetoencephalography.** This chapter covers the key concepts that MEG is based on. Starting with the source of MEG signals, measurable effects and characteristics of brain oscillations. We then cover data collection and analysis methods. This includes cryogenic MEG, along with SQUID sensor design and operation. Following this, the theory and implementation of MEG signal processing techniques is described in detail.

- **Chapter 3 – Optically pumped magnetometers.** In this chapter, we provide an in-depth examination of optically pumped magnetometers (OPMs), detailing the fundamental physics and principles behind their operation. The discussion covers the mechanisms of optical pumping and magnetic resonance, explaining how these processes enable the detection of extremely weak magnetic fields. Additionally, we cover the design and functionality of QuSpin's triaxial OPMs, used for all of the experimental work presented in this thesis. This chapter serves to establish a comprehensive understanding of OPM technology, setting the stage for the subsequent experimental investigations on shielding and sensor calibration.
 - **Chapter 4 – Signal processing in MEG.** This chapter outlines the key signal processing methods utilised for MEG data analysis. Starting with preprocessing steps including filtering, artifact removal, and homogeneous field correction. The main sections describe source signal reconstruction; these cover the main concepts involved in the beamforming such as the inverse problem and forward modelling. The chapter concludes with burst analysis, describing methods for detecting neural events using a Hidden Markov Model.
 - **Chapter 5 – Magnetic shielding.** This chapter delves into the magnetic shielding techniques employed in OPM-MEG. First describing passive magnetic shielding, which utilizes mu-metal—metal with high magnetic permeability—to attenuate external magnetic fields. Additionally, we discuss active magnetic shielding methods, including the use of both bi-planar and matrix coil systems. These are calibrated using a spherical harmonic model to precisely counteract residual magnetic fields. The use of these shielding techniques ensures an optimal low-field environment, crucial for the accurate operation of OPMs.
- **Experimental work**
 - **Chapter 6 – The role of beta bursts in top-down inhibition of somatosensory cortex: an OPM-MEG study.** This study explores the use of OPM-MEG to measure attentional modulation of beta oscillations in the somatosensory cortex. By presenting 'braille-like' patterns to participants and

monitoring their brain responses, we observed significant decreases in beta amplitude during attended stimuli, especially during attentional cues. Additionally, we found that attention affects the occurrence of pan-spectral bursts, which underlie beta rhythms. These findings highlight the effectiveness of OPM-MEG for non-invasive electrophysiological measurements and enhance our understanding of brain function.

- **Chapter 7 - Compensating motion artefacts in wearable magnetoencephalography with matrix coil active magnetic shielding.** Here we describe a new type of active shielding system for OPM-MEG which is comprised of 96 square unit coils arranged around the inner volume of an MSR. We demonstrate how to compensate magnetic fields in regions which can be flexibly placed between coils. Through the integration of optical tracking with OPM data acquisition, field changes induced by participant movement are cancelled with low latency (25 ms). High-quality MEG source data were collected despite the presence of significant (65 cm translations and 270° rotations) ambulatory participant movements.
- **Chapter 8 – Novel calibration Methods for Optically Pumped Magnetometers in wearable MEG.** In this study, we focus on the calibration of OPMs to enhance their accuracy and reliability in measuring magnetic fields. Two distinct methods were employed: a halo-like disc with a set of current dipoles and a matrix coil system designed for active magnetic shielding. The halo-like disc method utilizes precise current dipoles to generate controlled magnetic fields, providing a benchmark for OPM calibration. The matrix coil system, which uses a spherical harmonic model for calibration, actively mitigates external magnetic interference, thereby improving the precision of the OPMs in dynamic environments. Our findings demonstrate the effectiveness of both methods for calibration, highlighting their potential applications in various fields requiring high-fidelity magnetic field measurements.

- **Summary and outlook**

This section provides a summary of the experimental work and results. We discuss how the outcomes of the experimental

chapters align with the aims of this thesis. It concludes with a summary of the contribution to knowledge made by this thesis as well as a discussion of future objectives of OPM-MEG research within the context of the work presented here.

Chapter 2 Magnetoencephalography

In this chapter, the key concepts and ideas involved in MEG are introduced. The electrophysiological basis of MEG signals, along with their measurable effects and characteristic behaviour in relation to brain function are introduced. We then cover the physics involved in detecting such signals. First describing the traditional cryogenic MEG sensors, their design and operation, as well as some of their limitations. Finally, we describe some of the signal processing techniques relevant to the experimental work carried out in this thesis.

2.1 The source of the MEG signal

The cortex of the human brain is made up of approximately a hundred billion neurons, each connected to around ten thousand others. Although there are many more types of cell involved, neurons and glial cells are the fundamental components of the brain. While glial cells provide support and sustenance, neurons are responsible for sending and transmitting signals. It is the interactions between neurons that enable complex cognitive functions, such as learning, memory, and decision-making. These interactions are based on the movement of ions between the intra and extracellular medium. Maxwell's equations dictate that any movement of charges will in turn create a magnetic field. Magnetoencephalography (MEG) is based on the non-invasive measurement of these fields, which are observable outside the head if enough neurons act simultaneously. Here, we cover the biological and physical basis of MEG.

2.1.1 Neurons and action potentials

There is a large variety of neurons, with different types depending on their shape and function. However, their anatomy has some common features. As illustrated in Figure 2.1A, this includes the cell body (soma) from which the dendrites branch out and one axon, a long tail extending from the main body towards neighbouring cells. The axon is covered by a myelin sheath, which is a fatty layer that insulates the axon and increases the speed of electrical signal transmission. The myelin sheath is formed by a specific type of cell called a Schwann cell. The connections to other neurons are called synapses, specialized junctions that enable the transmission of electrical or chemical signals. The latter are delivered via the release of chemicals known as neurotransmitters. The soma contains the typical cellular components such as a nucleus, mitochondria, and ribosomes, as well as specialized organelles like synaptic vesicles, which are essential for neurotransmitter secretion. The dendrites are branch-like structures which connect the neuron to adjacent cells and can receive incoming signals.

Depending on the state of the neuron, signals can then travel down the axon and transferred to subsequent neurons.

Figure 2.1B shows one of the first illustrations of human neurons in the cortex, published by Santiago Ramon y Cajal in 1904. Considered by many as the father of modern neuroscience, he was the first to postulate the existence of individual neurons, even predicting the direction in which signals travelled down the body of the cells, as indicated by the arrows in his drawing. In terms of anatomy, neurons can be identified by their shape and dendrite distribution. Stellate neurons have a symmetrical dendrite distribution around the cell body (Figure 2.1C). On the other hand, pyramidal neurons have an uneven dendrite distribution, with most of the dendrites perpendicular to the cortical surface and a long axon extending from their bodies (Figure 2.1B). It is this difference in symmetry that is believed to make pyramidal neurons the main contributors to the MEG signal. Whereas for groups of stellate neurons the magnetic fields from opposing dendrites cancel out, in pyramidal cells, the magnetic fields from the uneven distribution of dendrites add constructively, producing a net magnetic field at a distance.

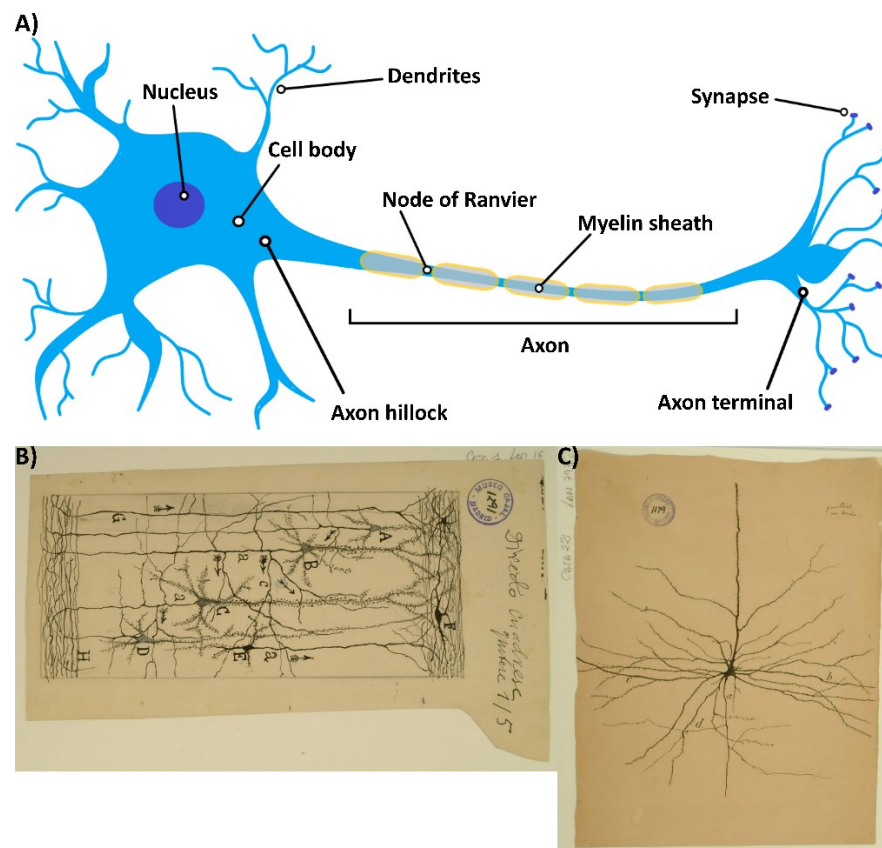


Figure 2.1: **A)** Anatomy of a typical cortical neuron. **B)** Ramon y Cajal's scientific drawings of nervous plexuses connected to pyramidal neurons and **C)** large stellate neuron in the motor cortex, observed under a microscope using Golgi staining (Legado Cajal. CSIC).

It is important to clarify what “signals” mean in this context. Brain activity is characterised by a set of electrophysiological processes, which can range from microscopic signals within a single neuron to local field potentials (LFPs) which are measurable across large cell populations. If we consider a single neuron, we find the most basic of all these phenomena, the action potential. Simply put, this consists of rapid changes in electrical potential propagating along the neuron’s membrane and down its axon. Starting with an imbalance in ion concentrations between the inside and outside of the neurons, this phenomenon is a consequence of the neuronal membrane’s unique ability to alter its permeability to different species of ions (Figure 2.2). Ion pumps and voltage gated channels in the membrane control the movement of ions such as sodium and potassium, increasing the number of cations outside the cell. This concentration gradient translates into an electrostatic potential, called the resting potential (typically ~ -70 mV). External stimuli can then decrease the magnitude of this potential, which can, in turn, open the ion channels if it meets a certain threshold (~ -55 mV). Sodium ions can then come back into the neuron. This will trigger the depolarisation of the cell, which acts as a travelling signal, opening ion channels along the axon of the neuron. This process is depicted in Figure 2.2B, showing the temporal evolution of a typical action potential for a human neuron. The resting potential for a given ion can be estimated using the Nernst equation

$$E_m = \frac{RT}{zF} \ln \left(\frac{[ion^z]_{out}}{[ion^z]_{in}} \right), \quad [2.1]$$

where R is the ideal gas constant, T is the temperature in Kelvin, z is the valency of the ion (1 for potassium, 2 for sodium) and $[ion^z]_{out/in}$ is the concentration of that ion outside or inside the cell. This expression holds true when the membrane is only permeable to one ion and there is no net flux of ions. Therefore, it can be a good approximation since potassium is the main contributor to the resting potential. In practice, the neuron’s membrane is permeable to more ions which contribute to the electrostatic potential along with several proteins and phosphates that live inside the cell. For a more accurate estimate, one can use the Goldman-Hodgkin-Katz (GHK) voltage equation, which can account for several different ion species (Goldman, 1943). This expression defines the membrane potential as

$$E_m = \frac{RT}{F} \ln \left(\frac{\sum_i^n P_{M_i^+} [M_i^+]_{out} + \sum_j^m P_{A_j^-} [A_j^-]_{in}}{\sum_i^n P_{M_i^+} [M_i^+]_{in} + \sum_j^m P_{A_j^-} [A_j^-]_{out}} \right), \quad [2.2]$$

where P_{ion} is the permeability, which describes how well an ion channel can permit the passage of different ions in meters per second, M and A are the concentrations of positive and negative monovalent ion species in moles per cubic meter, respectively. This formula sums over the contribution of each ion species that the membrane is permeable to, with each contributing term being similar to the Nernst potential. For example, if we try to estimate the contribution from sodium ions alone, we find that

$$E_{m,Na} = \frac{RT}{F} \ln \left(\frac{P_{Na}[Na^+]_{out}}{P_{Na}[Na^+]_{in}} \right) = \frac{RT}{F} \ln \left(\frac{[Na^+]_{out}}{[Na^+]_{in}} \right). \quad [2.3]$$

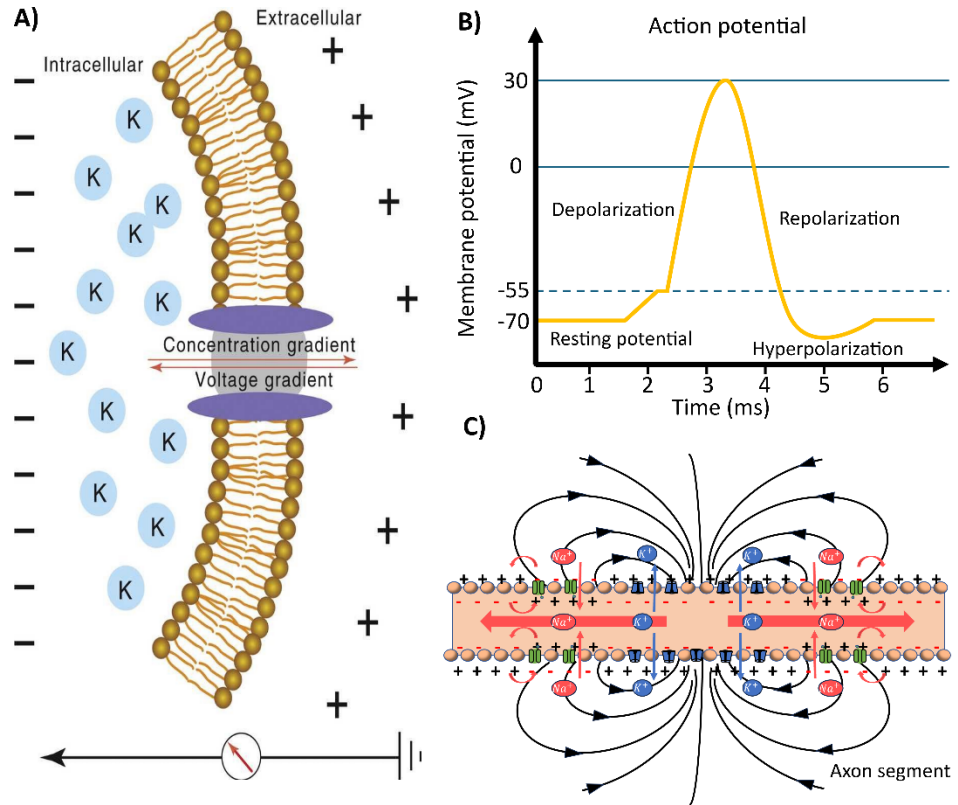


Figure 2.2: A) Ion concentration diagram across the neuronal membrane. Adapted from Squire, 2012. B) Temporal evolution for a typical action potential. C) Axon segment as the action potential travels down the membrane.

A simple diagram of how the action potential travels down the axon is shown in Figure 1.3C, opening different ion channels along its path. As shown above, sodium ions rush in, depolarising the membrane. Following this, potassium ion channels open to restore the resting membrane potential. The movement of ions acts as two opposing current dipoles, which can be thought of as a current quadrupole. Unlike the magnetic field produced by a dipole, which is inversely proportional to the square of the distance to the source, the field produced by a quadrupole decreases as $1/r^3$. In addition, action potentials only last around 1 ms, making it unlikely for an assembly of neurons to synchronize and fire together, which could potentially make the field detectable. This supports the notion that action potentials are not a major contributor to EEG or MEG signals (Hämäläinen et al., 1993). Nonetheless, they should not be completely removed from the picture, as some evidence suggests that synchronised action potentials may contribute to magnetic fields of much higher frequency, of the order of ~ 600 Hz (Curio et al., 1994; I. Hashimoto et al., 1996).

2.1.2 Beyond the action potential

The action potential is the main basis for neuronal interaction. When it reaches the end of an axon, it prompts the release of neurotransmitters into the synaptic cleft. Depicted on in Figure 2.3, this is the gap between the end of the axon of one neuron and the dendrite or cell body of an adjacent neuron (or post-synaptic cell). The molecules released can attach to the cell's membrane and open chemically gated ion channels in the adjacent neuron. This event can increase the intracellular potential in the post-synaptic neuron, termed PSP, in which case it is called an excitatory post-synaptic potential (EPSP), or decrease it, making it an inhibitory post-synaptic potential (IPSP). Figure 2.3 depicts this process for both cases. An EPSP is characterised by the release of excitatory neurotransmitter such as glutamate. It binds to receptors in the post-synaptic membrane, opening chemically gated ion channels that allow the flow of cations such as sodium ions into the cell. This will slightly depolarise the membrane, increasing the likelihood of an action potential in the post-synaptic cell. An IPSP produces the opposite effect, further polarising the cell thanks to inhibitory neurotransmitters, such as GABA. This will make the post-synaptic cell less likely to fire.

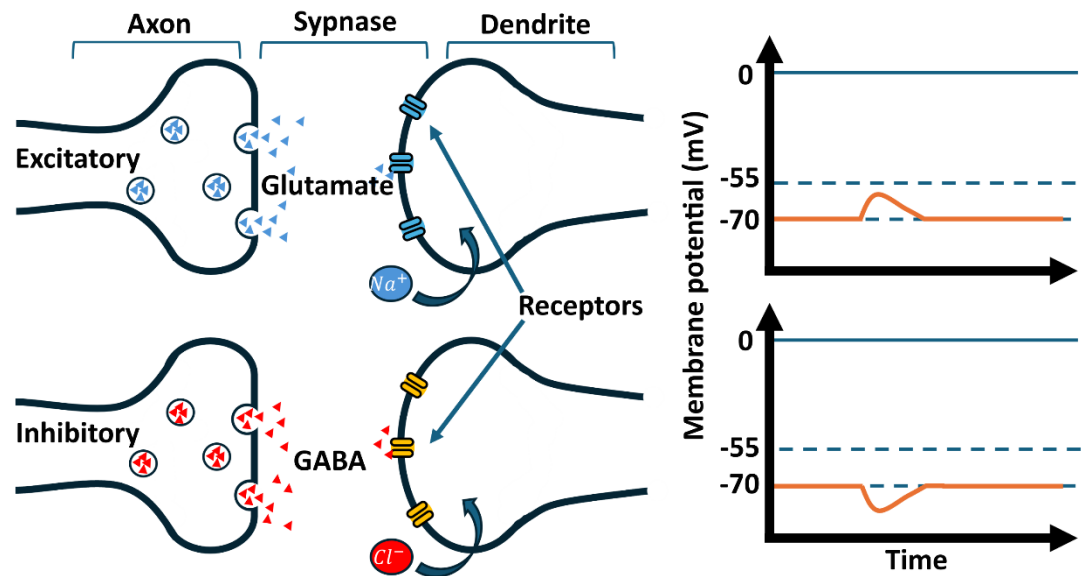


Figure 2.3: Diagram illustrating the process behind *excitatory* (top) and *inhibitory* (bottom) post-synaptic potentials. The uptake of neurotransmitters by the post-synaptic neuron can open ion channels, altering the membrane potential as show on the graphs on the left-hand side.

Overall, no single post-synaptic potential can trigger the action potential. It is the temporal and spatial combination of all the incoming synapses that will dictate the state of the post-synaptic neuron. If the sum of all the synaptic potentials meets the critical threshold, then an action potential will be triggered. In this way, neurons act as integrators.

Post-synaptic potentials across many dendrites result in a net flow of ions into or out of the neuron. This flow creates electrical currents travelling along the dendrites and into the post-synaptic neuron, decreasing in strength the further they get from the synapse. These are known as dendritic or primary currents. Unlike the action potential, they behave like current dipoles aligned along the dendrite, producing a magnetic field strength that decreases in strength with the square of the distance to the source ($1/r^2$). Furthermore, PSPs occur on longer timescales than action potentials depending on the type of neurotransmitter involved and the specific receptor dynamics at the synapse. With lifetimes ranging from 5 milliseconds up to tens of milliseconds, it becomes more likely for ensembles of neurons to act in synchrony, producing a stronger magnetic field at a distance than that from action potentials. This makes PSPs the main candidate for the source of the MEG signal.

A simple calculation can be performed to show how plausible this is, giving us an estimate of the number of synapses that could be involved in the generation of a measurable MEG signal (Hämäläinen et al., 1993). First, we consider the PSP to be a current dipole pointing along the dendrite which can be modelled as a round wire. We define the dipole strength as

$$Q = I\lambda. \quad [2.4]$$

For a PSP of voltage ΔV with a current I going through the synapse and a length decay constant λ . The current is given by

$$I = \frac{\Delta V}{r_s \lambda}, \quad [2.5]$$

where r_s is the resistance of the intracellular fluid per unit length. The exponential decay the current source experiences as it moves further from the synapse is defined by

$$\lambda = (\sigma_m r_s)^{-1/2}, \quad [2.6]$$

where σ_m is the membrane conductance (Scott, 1982). Assuming a cylindrical shape, the resistance of a dendrite of diameter d is

$$r_s = \frac{4}{\pi d^2 \sigma_{in}}, \quad [2.7]$$

where σ_{in} is the intracellular conductivity. Using all the above to make the appropriate substitutions into equation 2.4, we find that

$$Q = \frac{\pi d^2 \sigma_{in}}{4} \Delta V. \quad [2.8]$$

Using typical values for a single PSP, $d = 1 \mu m$, $\sigma_{in} = 1 \Omega^{-1} m^{-1}$ and $\Delta V = 25 mV$ (Scott, 1977), results in a dipole of strength $Q \approx 20 fAm$. Experimentally, magnetic field strengths measured outside the head are normally in the femtotesla (fT) to picotesla (pT) range. For a 1pT measurement, a source with a current-dipole moment of $\sim 10 nAm$ would be required. This tells us that that the source would involve around a million synapses to activate in synchrony. Pyramidal neurons can have thousands of synapses, and they populate the cortex with a density of around 10^5 cells per mm^2 . Our estimate therefore suggests that this would be more than enough to produce a measurable field. This, however, is too optimistic since the generated fields can be diminished by regions with current flowing in opposite directions so a larger area of activation would be required. Experimental data supports this, with values suggesting areas as large as $40 mm^2$ would be required to generate such fields (Chapman et al., 1984).

In a similar manner to the action potential, the flow of ions induced by a PSP is countered by a return to resting potential. The membrane restores the ion concentration gradient by expelling or intaking ions. As depicted in Figure 2.4, the resulting electric field between the ion intake and output points produces a volume current in the extracellular medium. As shown in the upcoming sections, this distinction will prove useful when producing the models used in MEG to process the measured signals.

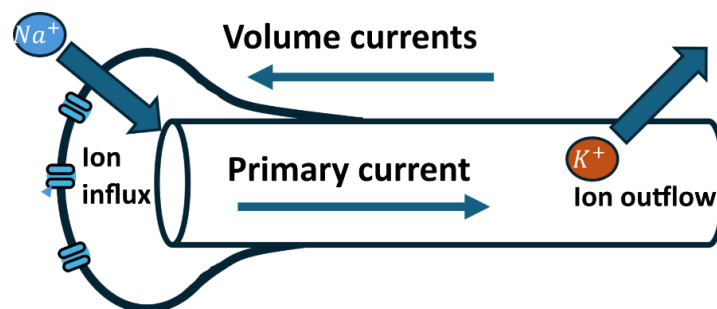


Figure 2.4: Diagram showing how *dendritic currents* can induce *volume currents* in the intracellular medium.

In essence, we find that differences in neuronal anatomy, geometry and orientation, and the synchronization of electro-chemical processes are key to understanding how magnetic fields are generated outside the brain. The quadrupole geometry of action potentials and their short lifetimes make them an unlikely contributor to the extracranial magnetic fields. On the other hand, post-synaptic currents are a stronger source due to their dipole-like field pattern and longer lifetimes. The main source of the MEG signal is therefore likely the synchronous postsynaptic activity of thousands to millions of pyramidal neurons

in the cerebral cortex. These neurons generate primary currents that produce magnetic fields detectable outside the head, allowing MEG to measure brain activity non-invasively with high temporal resolution. Incidentally, the energy required for the ion pumps constitutes $\sim 70\%$ of the energy used by the brain (Engl and Attwell, 2015; Rangaraju et al., 2014). This ties dendritic currents to metabolic metrics like fMRI, showing that MEG signals are theoretically linked to fMRI. Neural activity generates a range of measurable effects beyond the electromagnetic signals captured by MEG. For example, the influx of calcium ions, pivotal for neurotransmitter release, can be visualized through calcium imaging techniques, offering a glimpse into the dynamics of neuronal communication. As previously described, changes in blood oxygenation or glucose metabolism, provide indirect markers as well. We now discuss the measurable phenomena most relevant to MEG.

2.1.3 Local field potentials

LFPs reflect the summed electrical activity from a population of neurons within a specific volume in the brain, offering insights into the local synaptic and dendritic activity. They were first measured in the early 20th century by pioneers in electrophysiology such as Edgar Adrian and Richard Caton. Using basic amplifiers and recording equipment, they demonstrated that electrical activity could be recorded from the surface of the brain. In contrast to EEG, recording of LFPs involves the use of electrodes placed directly on or in the tissue of interest, allowing accurate recordings of the electrical activity within a very small region as shown in Figure 2.5A. The direct placement of the electrodes in the tissue allows the study of transmembrane current flow in ensembles of neurons in very small and specific regions (Eccles, 1951; Lorente de No, 1947). LFP measurements provide a wealth of information about brain activity, as they can capture subthreshold events that precede and contribute to the generation of action potentials (Bullock, 1997). They can provide a much closer and detailed look at some of the signals measured with other techniques, as shown in Figure 2.5B. While there is ongoing debate about the precise processes contributing to LFPs and the extent of their spatial localization, their utility in neuroscience research remains undisputed (Kajikawa and Schroeder, 2011; Katzner et al., 2009). For example, it has been shown that LFPs are closely linked to the hemodynamic changes measured in fMRI (Logothetis et al., 2001), with similar work showing that they also underpin MEG and EEG signals (Murakami and Okada, 2006).

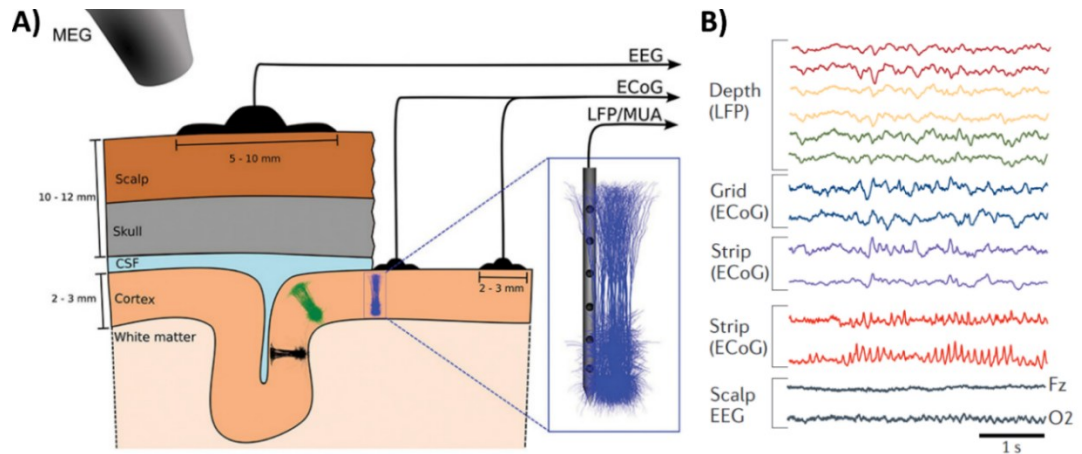


Figure 2.5: **A)** Diagram illustrating how different recording devices (MEG, EEG, electrocorticography and LFP electrodes) are placed relative to the head. Adapted from Hagen et al., 2018. **B)** Typical traces obtained from a patient with drug-resistant epilepsy using different recording methods. Adapted from Buzsáki et al., 2012.

LFP measurements are conducted through various means, depending on the research context. In humans, these recordings always necessitate invasive procedures, typically being performed during neurosurgical operations when the brain is exposed. A diagram of sensor placement for different direct neuroimaging techniques is shown in Figure 2.5A. The most common technique is known as electrocorticography (ECoG), since it involves placing electrodes directly on the cortical surface. More detailed measurements across the cortical layers can be obtained with depth electrodes, inserted directly into the brain. Invasive LFP recordings are even more prevalent in animal studies, where they have provided many insights the functionality of different brain regions. (Buzsáki et al., 2012). Although recent developments show promise for non-invasive recording of intracranial field potentials (Seo et al., 2015), the need for surgery for this type of recording presents significant practical limitations, making it only suitable for subjects requiring surgery or Deep Brain Stimulation (DBS) implants.

The relationship between LFPs and MEG signals is both intricate and fundamental to our understanding of brain electrophysiology. While LFPs are typically measured invasively, MEG non-invasively captures similar neural dynamics at a larger scale. As shown in the previous section, MEG signals primarily originate from the synchronous postsynaptic currents in the dendrites of pyramidal neurons, which are the same events that dominate LFPs (Hämäläinen et al., 1993). However, MEG is most sensitive to tangential sources in the cortical sulci, whereas LFPs can capture activity from all cortical orientations. Despite these differences, studies have shown strong correlations between simultaneously recorded LFPs and MEG signals, particularly in the lower frequency bands (Zhu et al., 2009). This correlation not only highlights the importance of LFP research for interpreting MEG data but also emphasizes

the significant benefits of using multiple neuroimaging techniques in parallel to obtain a deeper understanding of brain function.

2.1.4 Measurable effects

Regardless of the technique used to capture electrophysiological signals, understanding the brain's response to specific events often involves analysing fluctuations in the measured fields or potentials. These fluctuations have been consistently shown to correlate strongly with various cognitive processes and abilities. This leads us to the study of evoked and induced responses, two distinct but related phenomena. These responses reveal how sensory inputs, cognitive processes, and motor actions are mediated by the brain's electrical activity. This section provides an overview of the basic characteristics of measurable brain signals, and how these signals relate to brain function.

2.1.5 Spontaneous activity

Neural oscillations represent rhythmic or repetitive neural activity in the central nervous system. These oscillations are crucial for coordinating different brain regions, facilitating communication and integration of information across neural networks. By studying these rhythmic changes, researchers can gain a deeper understanding of the mechanisms underlying cognition, perception, and behaviour. First observed by Hans Berger in 1924 during some of the first EEG experiments (Berger, 1929), these oscillations occur naturally in the brain and persist at all times, independent of external stimuli or specific cognitive tasks. Also known as “spontaneous rhythms”, these neural oscillations are typically categorized into distinct frequency bands. Certain cognitive states and functions have been shown to modulate the phase and amplitude of specific frequency ranges. During task or stimuli processing, the abilities linked to modulating a specific frequency band are what is typically used to differentiate these bands (Mandal et al., 2018). For example, during some of his first EEG experiments, Berger observed that when subjects closed their eyes, there was a significant increase in the amplitude of brain oscillations in the 8-13 Hz (alpha) range (Berger, 1933). When subjects opened their eyes again, these oscillations became weaker. This effect, now known as alpha blocking, led to the identification of the alpha band and demonstrated how simple behavioural changes can modulate specific brain rhythms. These modulating effects tend to be very consistent and repeatable during experiments, providing reliable markers of specific cognitive processes. However, subtle individual variations exist, influenced by factors such as age (Saby and Marshall, 2012) or neurological conditions. The uniqueness and consistency of these patterns within individuals have even led to the development of 'neural fingerprinting' techniques for identifying individuals based on their brain oscillations (da Silva Castanheira et

al., 2021; Sareen et al., 2021). Work performed on this topic has led to the distinctive frequency bands known today:

- **Delta (0.5-4 Hz)** - Associated with deep sleep, unconsciousness, and certain pathological states (Bernardi et al., 2019; Riedner et al., 2007). It is also believed that delta modulation plays an important role in connectivity, inhibiting networks to help completion of specific tasks (Harmony, 2013).
- **Theta (4-8 Hz)** - Plays a crucial role in memory, particularly in memory encoding and retrieval (Jensen and Tesche, 2002; Onton et al., 2005). It is also associated with spatial navigation and emotional processing.
- **Alpha (8-13 Hz)** - Alpha rhythms are often linked to relaxed wakefulness and inhibition of task-irrelevant areas (Bauer et al., 2014; Klimesch et al., 2007). These oscillations typically increase in amplitude when eyes are closed and decrease during visual processing or attention tasks (Klimesch et al., 1998), suggesting a role in gating information flow and allocating cognitive resources.
- **Beta (13-30 Hz)** – Often linked to normal waking consciousness, active thinking, and focus. It's also associated with motor function and can be prominent during muscle contractions (Barone and Rossiter, 2021).
- **Gamma (30-100+ Hz)** - Gamma oscillations are thought to be involved in higher-order cognitive functions such as attention, perception, and consciousness (Jensen et al., 2007).

Abnormalities in these oscillatory patterns have been associated with various neurological and psychiatric disorders, making the study of neural oscillations not only crucial for understanding normal brain function but also for developing potential diagnostic tools and therapeutic interventions in clinical settings. A number of studies have shown how disorders like dementia, epilepsy or symptoms from traumatic brain injuries can affect neural oscillatory power and timing (Allen et al., 2021; Park and Hong, 2019; Rier et al., 2021; Tamilia et al., 2019). The study of neural oscillations requires MEG systems to have femtotesla sensitivity in the 1-100 Hz range. Some studies have reported oscillations in the range of 100-200 Hz (high gamma or epsilon band) and even up to 600 Hz in both animal models and human recordings (Curio et al., 1994; Isao Hashimoto et al., 1996). These ultra-high frequency oscillations may be involved in precise timing of neural firing and information encoding, opening new avenues for understanding the complexities of brain function.

2.1.6 Evoked responses

Evoked responses, also known as event-related potentials (ERPs) in EEG studies or event-related fields (ERFs) in MEG, are neural responses that are both time-locked and phase-locked to specific stimuli or events (Luck, 2005). These responses represent the brain's consistent electrophysiological reaction to a particular sensory, cognitive, or motor event. Figure 2.6 illustrates an example; we can see the amplitude change that constitutes the evoked response measured during a face-processing task. Due to the visual nature of the experiment, the field maps show the peak of this response is measured by sensors over the visual cortex. The first studies of evoked responses date back to the mid-20th century, starting with pioneering work by George D. Dawson who first recorded visual evoked potentials in humans using EEG (Dawson, 1947). In the realm of MEG, the first reported evoked responses were auditory evoked fields measured by Reite et al., 1978.

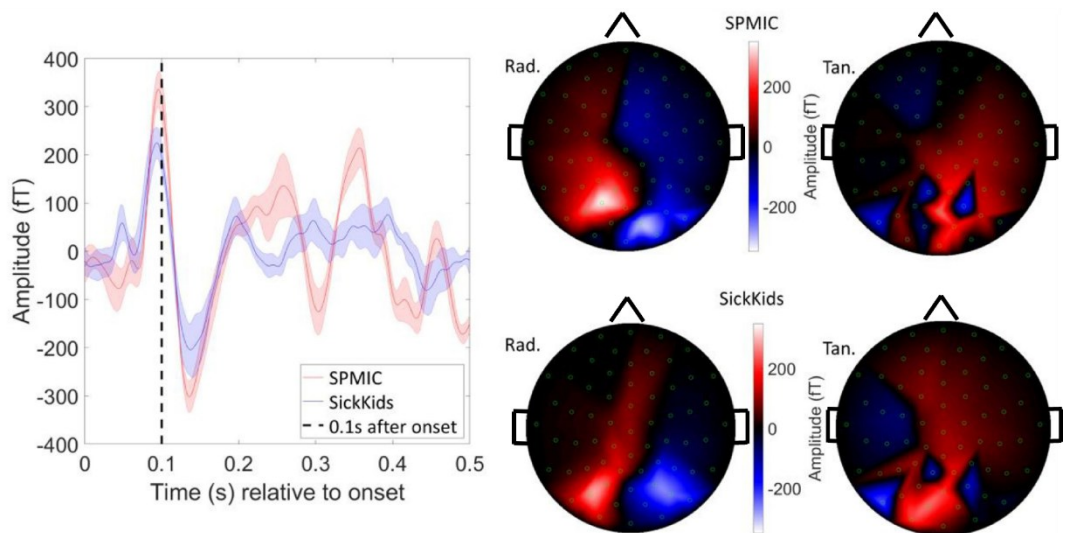


Figure 2.6: Sensor-level responses obtained during a face processing task (Hill et al., 2022). **Left:** Average response across 5 runs at two different OPM-MEG labs (Sir Peter Mansfield Imaging Centre (SPMIC) and SickKids hospital), with error bars indicating standard deviation. Dashed line marks 0.1s post-stimulus onset. **Right:** Field maps showing distribution at 0.1s peak response (Z-axis left, Y-axis right).

Evoked responses in both MEG and EEG are typically obtained by averaging multiple trials time-locked to the stimulus onset. This averaging process enhances the signal-to-noise ratio by emphasizing consistent neural activities while reducing random background noise (Picton et al., 2000). For a number of trials N , the reduction in noise through trial averaging can be estimated to be proportional to $\sim \sqrt{N}$, assuming Gaussian random distribution of noise. While EEG and MEG evoked responses often show similar temporal patterns, MEG offers superior spatial resolution and is particularly sensitive to tangential sources in cortical sulci (Hämäläinen et al., 1993; Hillebrand and

Barnes, 2002). The analysis of evoked responses has proven invaluable in understanding sensory processing, attention, language comprehension, and various cognitive functions. For instance, the N400 component, observable in both EEG and MEG, has been crucial in studying semantic processing (Kutas and Federmeier, 2011).

2.1.7 Induced responses

Induced responses are characterized by changes in the power or amplitude of specific frequency bands following a stimulus or event, usually without a consistent phase relationship across trials (Pfurtscheller and Lopes da Silva, 1999). As depicted on Figure 2.7A, this distinguishes them from evoked responses, which maintain phase consistency. These induced oscillatory changes can involve either increases (event-related synchronization, ERS) or decreases (event-related desynchronization, ERD) in power within particular frequency bands. For example, a tactile stimulus might induce a decrease in beta band power in motor cortex areas, reflecting enhanced local neural processing (Figure 2.7B).

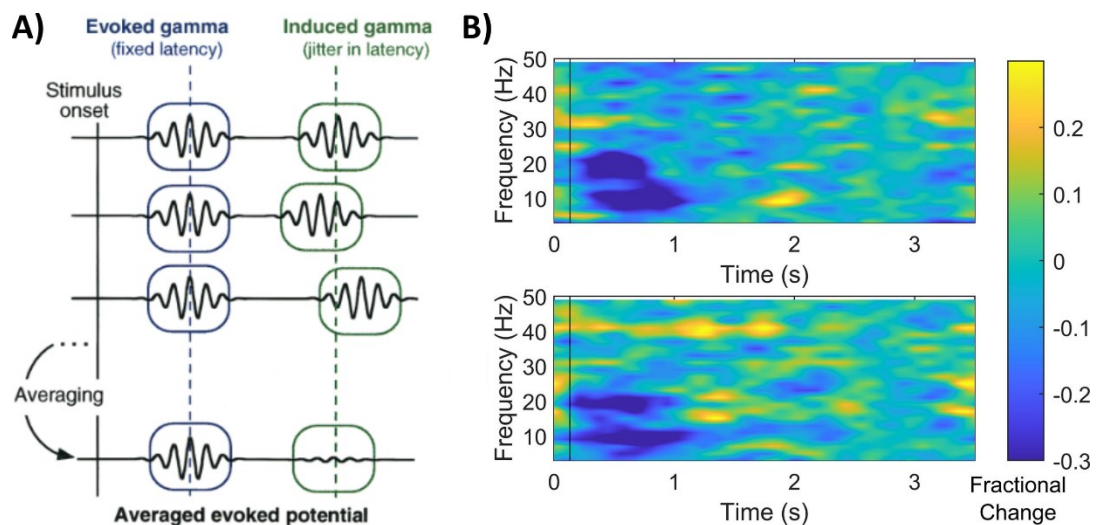


Figure 2.7 A) Trial averaging diagram of evoked and induced gamma responses. The evoked responses exhibit the same timing and phase across trials while the induced ones may vary. Adapted from Tallon-Baudry and Bertrand, 1999. **B)** Time-frequency spectra of neural oscillatory amplitude changes in left sensorimotor cortex from a single participant. Data shown for tactile stimulation of both fingers, extracted from the location of peak beta modulation. Colour indicates fractional change in spectral amplitude relative to baseline (measured 2.5-3s pre-stimulus). Vertical lines mark onset of first tactile stimulus. Adapted from Rier et al., 2024.

Induced responses are particularly valuable for studying cognitive processes that may not have a fixed temporal relationship to a stimulus, such as attention, memory retrieval, or decision-making. They have a very reliable and robust effect on brain signals and therefore, are pivotal for studying how the

brain dynamically reconfigures its functional networks in response to tasks or stimuli. Conventional averaging across trials may not be effective for studying induced responses. Methods for analysing induced responses often involve time-frequency decomposition techniques, such as wavelet analysis or Hilbert transforms. For this last method, signals are normally filtered to a specific frequency band, from which the amplitude envelope is obtained. The resulting envelope can then be averaged across trials to observe the oscillatory amplitude modulation induced by stimulation in the frequency band of interest. Induced responses can occur in multiple frequency bands simultaneously and can evolve over time, reflecting the complex, multi-scale nature of neural information processing. For instance, a cognitive task might induce an initial decrease in alpha power (reflecting reduced inhibition) followed by an increase in theta power (associated with memory engagement) and later gamma oscillations (linked to active information processing). Research on induced responses has been crucial in developing models of neural communication and information integration in the brain, such as the 'communication through coherence' hypothesis proposed by Fries, 2005. Their consistency makes them ideal to study certain neurological conditions; this is achieved by comparing responses between patients and healthy controls. For example, post-movement induced responses have been found to vary in people suffering from conditions such as schizophrenia (Gascoyne et al., 2020; Robson et al., 2016), autism (Gaetz et al., 2020) or multiple sclerosis (Barratt et al., 2017).

2.1.8 Functional connectivity

Although responses to stimuli can help study functionally distinct regions, it is the collective behaviour of multiple regions that underpins cognitive function. Specifically, it is the constant formation and dissolution of brain networks. Functional connectivity refers to the statistical dependencies between spatially distinct neurophysiological events, reflecting how different brain regions interact and coordinate their activity in networks (Friston, 2011). It can be measured using various methods, including correlation or phase synchronization of neural signals (Bastos and Schoffelen, 2015). A seminal model proposed by (Fries, 2005) suggests that long-range communication in the brain is facilitated when neuronal populations oscillate coherently with each other. This 'communication through coherence' hypothesis posits that coherent oscillations create optimal time windows for information transfer between brain regions.

In MEG research, functional connectivity analyses have provided valuable insights into brain network dynamics across different cognitive states and neurological conditions. For instance, Brookes et al., 2011, demonstrated the feasibility of detecting canonical resting-state networks (RSNs) using MEG, while Palva and Palva, 2012, reviewed how oscillatory synchrony supports the integration of distributed neural processing. Resting state networks (RSNs) are

patterns of functional connectivity observed when the brain is not engaged in a specific task. Initially discovered using fMRI these networks were further characterized through subsequent studies, notably by Raichle et al., 2001, who identified the default mode network, a “baseline” default mode of brain activity that seems to be consistently present during rest and suspended during goal oriented tasks. RSNs such as the default mode network, frontoparietal network, and sensorimotor network, exhibit coordinated activity even in the absence of external stimuli. MEG studies have provided unique insights into the temporal dynamics and frequency-specific characteristics of these networks (de Pasquale et al., 2010). The ability to study RSNs with the high temporal resolution of MEG has enhanced our understanding of how these networks rapidly reconfigure in response to cognitive demands and how they may be altered in various neurological and psychiatric conditions (Nugent et al., 2015). More recently, advanced techniques such as multivariate autoregressive models, graph theoretical approaches or Hidden Markov Models (HMMs) have been applied to MEG data to capture complex, time-varying connectivity patterns (O’Neill et al., 2018; Quinn et al., 2018).

2.2 Measuring brain signals: MEG

The field of magnetoencephalography traces its roots back to the 1960s, with the pioneering work of David Cohen. In 1968, Cohen first successfully measured the magnetic fields produced by alpha brain rhythms using a 1 million turn copper induction coil as a detector. However, these early measurements were extremely noisy and required extensive magnetic shielding. The real breakthrough came in 1972 when Cohen, working along with James Zimmerman, introduced the use of Superconducting QUantum Interference Devices to MEG recordings. SQUIDs, which rely on the principles of superconductivity, offered unprecedented sensitivity to weak magnetic fields. This innovation dramatically improved the signal-to-noise ratio of MEG measurements, allowing for the detection of spontaneous brain activity and evoked responses without averaging (Cohen, 1972). The introduction of SQUIDs marked a turning point in MEG technology, paving the way for its development into a powerful tool for non-invasive brain imaging. Here, we cover the physics involved in the operation and design of SQUIDs. Starting with superconductivity, many of the ideas that made such sensitive devices possible were born out of advances in quantum mechanics.

2.2.1 Superconductivity

Superconductivity has revolutionized modern science and medicine by enabling the creation of powerful electromagnets with example applications including MRI machines and particle accelerators, as well as highly sensitive magnetic field detectors like SQUIDs, which are crucial for MEG. The

microscopic theory of superconductivity, known as BCS theory (after Bardeen, Cooper, and Schrieffer), begins with the concept of Cooper pairs (Bardeen et al., 1957). In a superconductor, electrons can overcome their mutual repulsion and form weakly bound pairs called Cooper pairs. This pairing is mediated by phonons, the quantized vibrations of the crystal lattice. It all begins with a single electron moving through the material. As this electron travels, it pulls on the surrounding positively charged ions in the crystal lattice structure. This disturbance creates a phonon, which carries with it a slight increase in positive charge density. Now, imagine a second electron some distance behind the first. This trailing electron, rather than being repelled by its negatively charged counterpart ahead, finds itself attracted to the wake of positive charge left behind. This attraction can overcome the natural repulsion between the two electrons. It's a delicate balance, but under the right conditions, the phonon-mediated attraction wins out. The two electrons, despite their identical charges, begin to move in concert, bound together by the very vibrations of the crystal they inhabit. This only occurs when the effect of the electron moving through lattice becomes larger than thermally induced vibrations, which is why the very low temperatures are required.

Cooper pairs behave in remarkable ways. They typically adopt opposite spins and momenta, a configuration that allows them to maximize the benefits of their phonon-mediated attraction while minimizing their overall energy. This pairing isn't confined to a small space; it can extend over hundreds of nanometres, a vast distance on the atomic scale. Additionally, the formation of Cooper pairs is not an isolated event. As more and more electrons pair up, they create an environment that encourages even more pairings. It's a collective phenomenon, with each pair contributing to and benefiting from the overall effect. As this pairing occurs, a curious thing happens to the energy landscape of the material.

This transformation from individual electrons to Cooper pairs marks a fundamental shift in the material's behaviour. An energy gap opens up around the Fermi level, a forbidden zone that gives superconductors many of their unique properties. The paired electrons, now behaving like bosons rather than fermions, can collectively occupy the same quantum state, forming a coherent, macroscopic wave. This is analogous to the formation of a Bose-Einstein condensate but occurs at much higher temperatures due to the effective attraction between electrons. This macroscopic quantum state is described by a single wavefunction, often referred to as the 'superconducting order parameter' or 'condensate wavefunction'. The coherence of this state means that the Cooper pairs move in unison through the material, without scattering off impurities or lattice vibrations. This collective motion of Cooper pairs is responsible for the zero electrical resistance observed in superconductors.

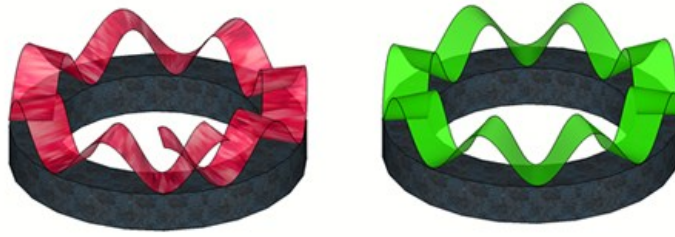


Figure 2.8: Wavefunction diagram around a superconducting ring. The phase change around the loop must be continuous, this makes the example on the left side impossible, only an integer number of cycles can be contained in the ring, as shown on the right-hand side. Diagram adapted from Mercier, 2011.

The energy required to break a Cooper pair creates an energy gap in the electron spectrum of the superconductor. This gap is typically on the order of MeV and is temperature-dependent, going to zero at the critical temperature T_c . The existence of this gap is crucial for many of the unique properties of superconductors, including their ability to exclude magnetic fields (the Meissner effect) and the occurrence of quantized magnetic flux in type-II superconductors. This last phenomenon is what enables such sensitive magnetic field measurements with SQUIDs. As illustrated in Figure 2.8, the macroscopic wavefunction of the electrons in a ring of superconducting material must be single valued. This means that if we were to measure the phase of the wavefunction along the ring, the phase should match after a whole revolution. If the ring is placed in a magnetic field, this continuity is only possible if the magnetic flux threading through the loop is quantized. This phenomenon introduces the unit of flux quantization, $\Phi_0 = 2.07 \cdot 10^{-15}$ Wb, also known as the flux quantum. The induced current (or “shielding current”) maintains a constant flux throughout the ring of magnitude $n \cdot \Phi_0$, for only integer values of n . If this current is measured and the inductance of the ring is known, one could therefore estimate the flux experienced by the superconducting ring. The flux quantum is very small, so much so that for a small loop, the current runs from minimum to maximum for a very small change in field. This, however, is not possible in practice since such a measurement would break the ring and the macroscopic wavefunction would vanish. Luckily, the wavefunction can tunnel through a thin enough layer of electrically insulating material thanks to the Josephson effect.

2.2.2 Josephson junctions

First predicted by Brian Josephson in 1962, the concept of the Josephson junction paved the way for the development of SQUID sensors (Josephson, 1962). As illustrated in Figure 2.9, this junction consists of two superconductors separated by a thin barrier of non-superconducting material. The barrier, often no more than a few nanometres thick, might be an insulator, a normal metal, or even a physical constriction in the superconductor itself. In quantum mechanics, particles can pass through barriers that would be insurmountable in the classical world, this also applies to Cooper pairs. The magic of the Josephson junction lies in its ability to allow Cooper pairs to tunnel through this barrier, usually an oxide layer.

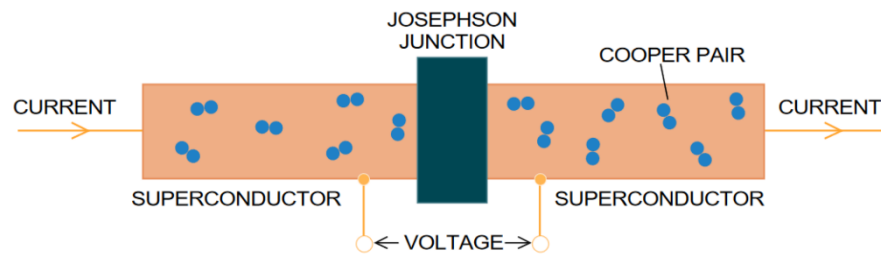


Figure 2.9: Diagram of a Josephson junction, illustrating how Cooper pairs can tunnel through a non-superconducting barrier generating a current.

When we consider the macroscopic wavefunction of the Cooper pairs on either side of the junction, we find that they can be described by a magnitude and a phase. The key insight of Josephson was to realize that the tunnelling current across the junction depends on the phase difference between these two wavefunctions. This is described as quantum interference, in which the interaction of both wavefunctions leads to two fundamental Josephson effects. The first, known as the DC Josephson effect, states that a supercurrent can flow across the junction even in the absence of any applied voltage. The magnitude of this current is given by the first Josephson equation:

$$I = I_c \sin \delta, \quad [2.9]$$

where I_c is the critical current of the junction and δ is the phase difference between the two wavefunctions on each side (known as Josephson phase). The critical current determines the maximum current that can flow through the junction, and it depends on the junction's size, the superconducting material and its critical temperature. The second effect, the AC Josephson effect, comes into play when a voltage is applied across the junction. In this case, the phase difference evolves in time, leading to an oscillating supercurrent. The frequency of this oscillation is precisely proportional to the applied voltage, with a conversion factor of 483.6 MHz per microvolt (Chesca et al., 2004).

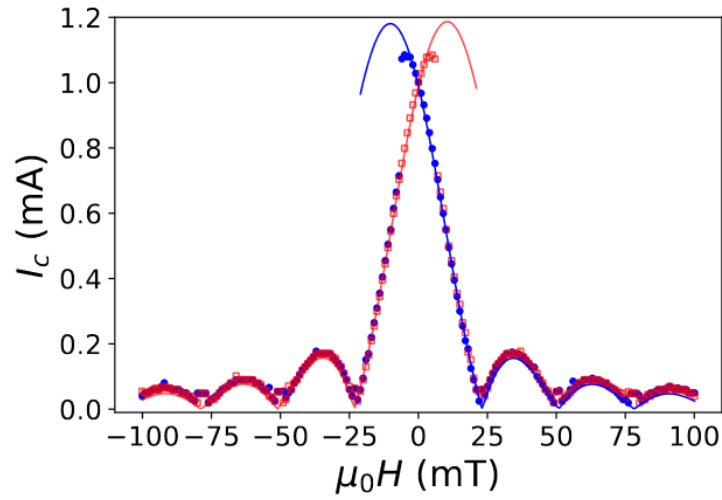


Figure 2.10: Experimental data obtained measuring the critical current as the applied magnetic field is varied through a ferromagnetic Josephson junction. Adapted from Mishra et al., 2023.

These effects make Josephson junctions highly sensitive to magnetic fields. A magnetic field threading the junction modifies the Josephson phase, which in turn alters the current flowing through the junction. This is a consequence of quantum mechanics, specifically, the Aharonov–Bohm effect, which states that the phase of a particle’s wavefunction is altered in the presence of a vector potential (Kasunic, 2019). The current I through the Josephson junction is affected by a vector potential $\mathbf{A}$ so that the Josephson equation becomes

$$I = I_c \sin \left(\delta + \frac{2q_e}{\hbar} \int \mathbf{A} \cdot d\mathbf{s} \right) \quad [2.10]$$

where q_e is the electron charge, $\hbar$ is the reduced Planck’s constant and the integral is performed across the junction (Feynman, 1965). Figure 2.10 illustrates quantum interference with a plot showing the current measured across a Josephson junction as the applied magnetic field is varied, modifying the critical current. This is the operating principle behind SQUIDs. Moreover, Josephson junctions exhibit the same quantum mechanical behaviour as a complete superconducting ring. The phase difference across a junction in a superconducting loop must be quantized in units of 2π , which again means that the current across the junction is sensitive to the number of flux quanta threading through it ($\Phi_0 = h/2e$).

2.2.3 The DC SQUID

The DC SQUID brings all the phenomena mentioned above to measure very small changes in the magnetic field it experiences (rather than its absolute value). A DC SQUID consists of a superconducting loop interrupted by two

Josephson junctions (Figure 2.11A). Two Josephson junctions are required since a single junction can only measure magnetic flux in discrete flux quanta. However, in a superconducting loop with two Josephson junctions (a DC SQUID), the situation is different. The total phase difference around the loop must still be an integer multiple of 2π , due to the quantization of magnetic flux. However, this means that the phase difference across each individual junction is not restricted to integer multiples of 2π . Instead, the phase difference across each junction can take on any value between 0 and 2π , depending on the magnetic flux threading the SQUID loop. This allows the critical current (I_c) of the SQUID to be modulated continuously as a function of the applied magnetic flux, rather than in discrete steps.

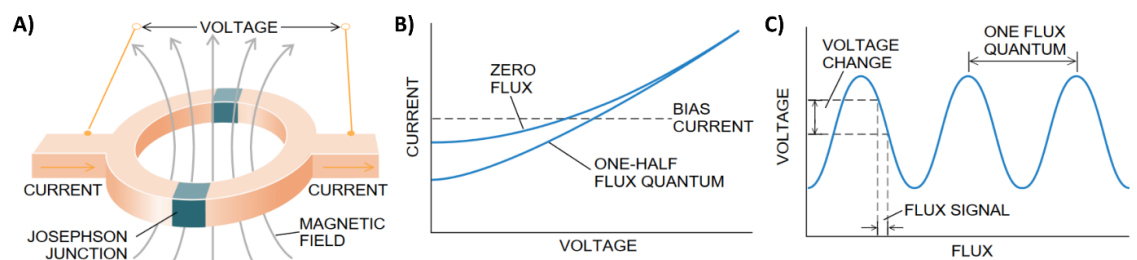


Figure 2.11: DC SQUID operation. A) Diagram showing DC SQUID design, with a bias current and the two Josephson junctions. B) Typical $I - V$ characteristic for a conventional DC SQUID. C) Voltage modulation across the Josephson junctions as a response to increasing magnetic flux. Adapted from Clarke, 1994.

The operation of a DC SQUID involves a specific set of steps. First, the superconducting loop is biased with a current I and exposed to an external magnetic field $H = B/\mu_0$. The two Josephson junctions limit the maximum supercurrent (I_c) that can flow through the ring. Crucially, I_c is modulated periodically by the magnetic flux threading through the SQUID loop, with a period of one flux quantum ($\Phi_0 = h/2e$). For practical measurements, the SQUID is biased with a current. If this bias current is above the critical current I_c , then a voltage is produced across the SQUID. The voltage (V) across the junctions is then measured as a function of the applied magnetic flux (Φ_a). As shown in Figure 2.11C, the applied flux alters the critical current, reaching a maximum for any integer number of flux quanta, including zero. I_c reaches a minimum for half integer numbers of flux quanta. In correspondence, this behaviour translates to a hysteresis curve when plotting current versus voltage, as shown in Figure 2.11. To measure small flux changes ($\delta\Phi_a$), the bias current is set to maximize the voltage modulation amplitude. The applied flux is typically set to $(2n + 1)\Phi_0$ (for $n = 0, 1, 2, \dots$) to maximize the flux-to-voltage transfer coefficient ($V_\Phi = |\delta V/\delta\Phi_a|$). Consequently, for a small applied flux signal $\delta\Phi_a$, the net resistance of the superconducting ring changes, producing a change in the output voltage signal $\delta V = V_\Phi \delta\Phi_a$ (Figure 2.12C). This configuration allows the DC SQUID to function as a highly sensitive flux-to-voltage transducer, capable of detecting extremely small magnetic fields.

In practice, DC SQUID design and operation can be even more complex. As discussed, the current-voltage characteristic of a Josephson junction is hysteretic. This can be avoided by adding a shunt resistance across the junction. The resistance helps to "overdamp" the junction, making the V-I curve non-hysteretic and single-valued. It also allows the SQUID to operate at higher bias currents, extending its dynamic range and the range of detectable magnetic fields.

Additionally, DC SQUIDs are normally used in Flux-Locked Loop (FLL) operation. This is done to achieve linear operation and extend the dynamic range of the SQUID while also solving the hysteresis problem. As shown in Figure 2.12A, the external magnetic field to be measured induces a current in the input coil, which is coupled to the SQUID loop. The flux change in the SQUID causes a voltage change across it. This voltage change is then amplified by a low-noise preamplifier. The amplified signal is fed into the integrator circuit, which generates a feedback current (see Figure 2.12B). Finally, the feedback current is applied to a feedback coil coupled to the SQUID, generating a magnetic flux that exactly cancels the initial flux change. Since this is proportional to the external field, the feedback current is the true output of the SQUID.

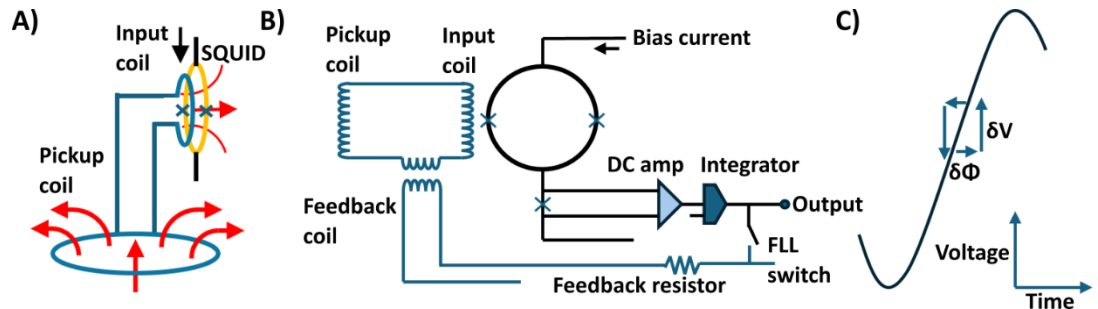


Figure 2.12: Coupled SQUID operation: A) Design diagram for a coupled SQUID. B) Simplified diagram of a circuit with a Flux-Locked Loop. C) Voltage response of a SQUID operated in FLL.

The negative feedback loop maintains the SQUID at a fixed working point on its periodic voltage-flux characteristic, ensuring a linear response over a wide range of input signals. The FLL configuration allows the SQUID to measure magnetic fields with extreme sensitivity, changes much smaller than a single flux quanta. Typically achieving resolutions on the order of femtotesla (10^{-15} T) in MEG applications. The use of FLL in DC SQUIDs enables these sensors to combine high sensitivity with a wide dynamic range, making them ideal for detecting the weak magnetic fields generated by neural activity in MEG studies. The dynamic range is defined by the device's tolerance threshold for magnetic fields, beyond which hysteresis or noise escalates. In terms of flux quanta, dynamic ranges of up to $8 \cdot 10^4 \Phi_0$ have been demonstrated experimentally, with some digital SQUID setups reaching up to $5 \cdot 10^6 \Phi_0$ (Haverkamp et al., 2011; Zimmermann et al., 1997). For other applications like MEG, the dynamic

range of the SQUIDs that are used is typically above 120 dB, with some commercially available systems going up to 192 dB (Vrba and Robinson, 2001).

Lastly, it is also important to note that the DC SQUID described above is known as an uncoupled SQUID. Due to its low inductance and small flux capture area ($\ll 1\text{mm}$), such a system has poor coupling to adjacent magnetic fields. This can be solved by introducing a second pickup loop, with a much larger area. These are typically placed in series, essentially coupling both superconducting loops so that any flux detected by the pickup coil will induce a current, in turn producing a secondary magnetic flux through the SQUID. As depicted on Figure 2.12A, this enables measurement of magnetic flux over a much larger area than that of the SQUID itself. Typically, the larger superconducting circuit is called a flux transformer, and it couples the very small SQUID to the relatively large coil near the scalp. Known as coupled SQUIDs, this is the common setup for MEG applications, with the pickup coil being the one closest to the scalp. This normally yields sensitivities of around $2\text{--}10\text{ fT}/\sqrt{\text{Hz}}$ when measuring the radial component of magnetic field (Vrba, 2000).

2.2.4 Noise reduction

Environmental magnetic noise poses a significant challenge in SQUID-based MEG systems due to their extreme sensitivity. As shown in previous sections, the fields produced by the human brain are extremely weak (fT to pT range). These can be around 6 to 8 orders of magnitude weaker than the Earth's magnetic field (~ 25 to $65\text{ }\mu\text{T}$). Potential sources of noise can include fluctuations in the Earth's magnetic field, urban electromagnetic interference from power lines and electronic devices, and even magnetic fields generated by elevators or passing vehicles. Figure 2.13A illustrates this by showing the relative magnitudes of various sources contributing to background noise. Biological sources can also appear in the data, examples include any muscle artifact such as eye blinks, jaw clenching, heart beats and any form of participant movement. These external fields mask the brain's weak magnetic fields. Consequently, effective noise reduction techniques are crucial for obtaining meaningful MEG measurements.

2.2.4.1 Magnetic shielding

The magnetic shielding employed in MEG systems is a key component that ultimately enables adequate SQUID operation. Magnetically shielded rooms constitute the passive shielding of the system, acting as a protective barrier by attenuating the external magnetic fields by several orders of magnitude. MSRs are typically constructed from layers of copper or aluminium and high-permeability materials (μ -metals) that redirect magnetic field lines around the

shielded volume. The mu-metal layers mitigate low frequency interference while the copper layers deal with higher frequency noise. There are several vendors that specialize in the design and construction of such rooms for use in MEG, namely Magnetic Shields Limited (MSL), Vacuumschmelze GmbH & Co. KG, Magnetic Shield Corporation and IMEDCO. The rooms provided by these companies can range in size and number of shielding layers. Figure 2.13B illustrates what a typical MSR looks like for MEG systems. While technical specifications may vary among vendors, MSRs generally share common features such as waveguides for cable passage and a projector hole for visual stimulus presentation. MEG systems generally require MSRs with 2 to 4 layers of μ -metal with varying sizes depending mainly on research needs, budget and site availability. Figure 2.13C shows a photo the construction process, which requires the precise alignment and contact required between metal sheets in each layer.

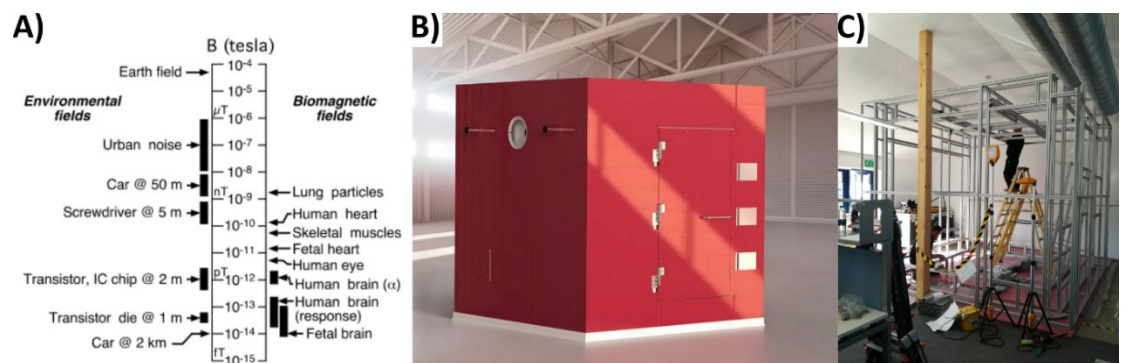


Figure 2.13: **A)** Magnetic field strength magnitude scale for different environmental and biomagnetic sources. Adapted from Vrba, 2000. **B)** Computer rendering of the MuRoom MSR, a product of Magnetic Shields Limited **C)** Photo showing the construction of the MuRoom located at the Sir Peter Mansfield Imaging Centre in Nottingham.

2.2.4.2 Gradiometers

Gradiometers are designed to measure the spatial gradient of the magnetic field rather than the field itself, effectively suppressing distant noise sources while retaining sensitivity to nearby brain signals. There are two main types of gradiometers used in MEG: axial gradiometers and planar gradiometers. As illustrated in Figure 2.14A, axial gradiometers consist of two coils wound in opposite directions, typically separated by a baseline distance of a few centimetres. They measure the difference in the magnetic field between these two points along the axis of the device. Planar gradiometers, on the other hand, measure the tangential derivatives of the magnetic field and consist of two coils in the same plane but with opposite orientations (Figure 2.14B). Both types are effective at reducing environmental noise, but they offer different sensitivity profiles and spatial resolutions (Hämäläinen et al., 1993). Some MEG systems, like the Elekta Neuromag TRIUX, incorporate planar gradiometers along with

magnetometers to provide comprehensive field measurements (Taulu et al., 2014).

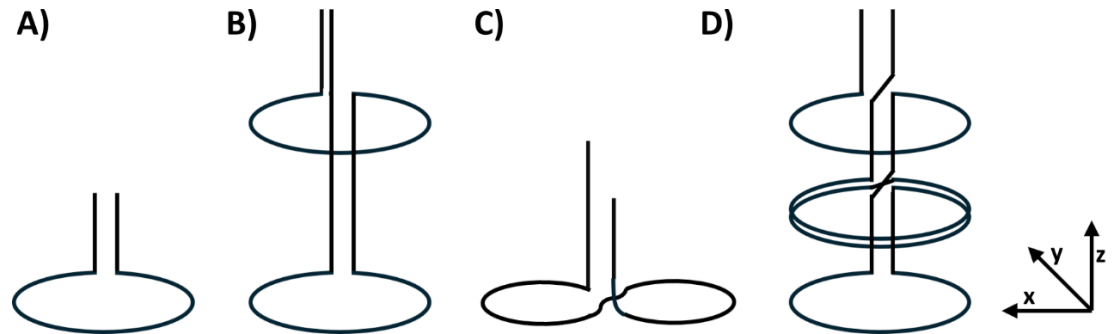


Figure 2.14: A) Magnetometer configuration B) Axial gradiometer C) Planar gradiometer D) Second order axial gradiometer.

The design of gradiometers capitalizes on the spatial characteristics of brain signals versus environmental noise. The pick-up coil, positioned close to the scalp, detects both the brain's magnetic fields and environmental interference. In contrast, the compensation coil is strategically placed farther from the head, where it primarily measures interference fields. This arrangement exploits the assumption that distant noise sources produce relatively uniform magnetic fields over the scale of the gradiometer, while brain signals vary more rapidly in space. By subtracting the signals from these two coils at the hardware level, gradiometers effectively attenuate homogeneous external fields while preserving the spatially varying fields generated by neural activity.

2.2.4.3 Synthetic gradiometers

Synthetic gradiometers offer an additional approach to noise reduction in MEG, typically implemented during post-processing (Fife et al., 1999). Unlike physical gradiometers, which are fixed configurations of pickup coils, synthetic gradiometers are implemented through software algorithms and reference vector magnetometers. This technique allows for flexible and adaptable noise reduction strategies, as researchers can adjust the virtual sensor arrangement and gradiometer order to best suit the specific noise profile of their data. For example, a first-order synthetic gradiometer is created by combining the outputs of two magnetometers separated by a known distance. The basic principle involves subtracting the output of one magnetometer from another to cancel out common-mode noise.

Consider a reference vector magnetometer with one coil measuring each axis k of the magnetic field. Assuming all three coils have the same gain α_r , its output can be described as $\mathbf{R}_k = \alpha_r \mathbf{B}_k$, where $\mathbf{B}_k$ is the magnetic field

experienced by each coil. Similarly, the primary magnetometer near the participant's head outputs $m_p = \alpha_p(\mathbf{p} \cdot \mathbf{B}_0)$, where α_p is again the gain of the sensor, $\mathbf{p}$ is the unit vector normal to the pickup coil and $\mathbf{B}_0$ is the field at the centre of the sensor. If we project the reference output to the primary sensor's vector $\mathbf{p}$, then we can subtract the reference signal to obtain a first order synthetic gradiometer given by

$$g = m_p - \frac{\alpha_p}{\alpha_r}(\mathbf{p} \cdot \mathbf{R}) = \alpha_p \mathbf{p} \cdot (\mathbf{B}_0 - \mathbf{B}) = \mathbf{p} \mathbf{G} \mathbf{b}_1, \quad [2.11]$$

where $\mathbf{G}$ represents the primary gradient tensor, while $\mathbf{b}_1$ denotes the baseline vector of the first-order gradiometer. Higher order gradiometers extend this concept by using more sensors and more complex subtraction schemes. The difference between the measurements from different pairs of sensors within this array can be combined to create a higher-order gradient.

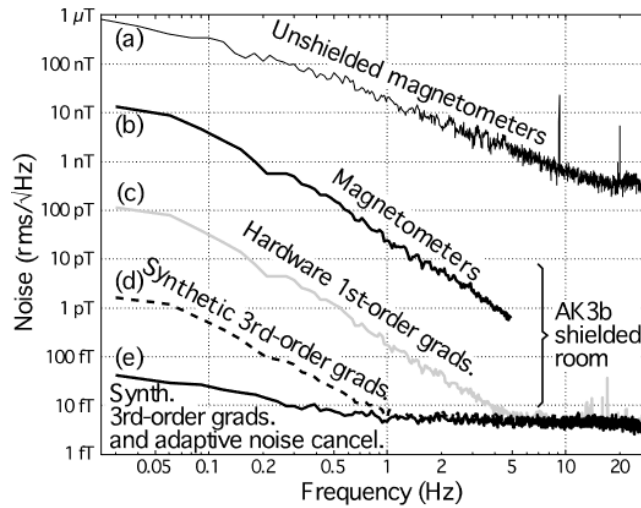


Figure 2.15: Noise floor level at different stages of noise reduction, lines a) and b) show unshielded and shielded magnetometer data, respectively. Lines c), d) and e) showcase the effect of hardware and synthetic gradiometers. Adapted from Vrba, 2002.

The primary advantage of synthetic gradiometers lies in their ability to enhance data quality by effectively reducing both environmental and physiological noise. Figure 2.15 demonstrates how much of an improvement in noise floor levels this technique can obtain, especially when employed along with shielding and hardware gradiometers. By combining signals from multiple sensors in software, synthetic gradiometers can achieve noise cancellation similar to that of hardware gradiometers, but with the added benefit of being able to optimize the noise reduction for each specific dataset or experiment. This flexibility makes synthetic gradiometers particularly useful in situations where hardware gradiometers may be limited or unavailable, such as in some types of OPM-MEG systems. Moreover, the ability to apply synthetic gradiometers

retrospectively allows researchers to experiment with different noise reduction strategies without the need for additional data collection. On the other hand, it is important to note that the subtraction process used in creating synthetic gradiometers can actually amplify random noise. If we consider the random noise in each sensor to be independent and have a standard deviation of σ , then for a first-order gradiometer the resulting noise is $\sqrt{2}\sigma$. This increase is usually outweighed by the benefits of reducing other types of noise, leading to an overall improvement in data quality.

2.2.5 Available SQUID-MEG systems

The market offers various MEG systems that employ SQUID technology. These devices commonly incorporate a helmet-shaped sensor array designed to envelop the participant's cranium. Figure 2.16A illustrates a typical setup, featuring the sensor-equipped dewar housed within an MSR. External to the room, the diagram depicts key components of the system. These include the MEG console, which performs the analog-to-digital conversion of the measured signals, as well as the acquisition and stimulus computers. To illustrate this, Figure 2.16B provides a photograph of an actual SQUID-MEG system built by CTF Technologies, Inc and housed in a room built by Vacuumschmelze. Some of the most widely used MEG system providers include:

- Elekta Neuromag TRIUX: This company, now part of MEGIN (Helsinki, Finland), offers systems with 306 channels, combining 204 planar gradiometers and 102 magnetometers. This provides high sensitivity and spatial resolution, making it suitable for both clinical and research applications.
- CTF MEG (Coquitlam, Canada): CTF systems typically feature 275 axial gradiometers, known for their excellent noise cancellation properties. They also offer optional reference channels for additional noise reduction.
- Yokogawa/KIT (Tokyo, Japan): These systems offer various configurations, with their latest models featuring up to 440 channels. They are known for their compact size and high sensitivity.
- Compumedics (Victoria, Australia): Compumedics offers a range of MEG systems, including the Orion Lifespan system, which features two separate sensor arrays of different sizes for scanning paediatric and adult populations (86 and 138 sensors, respectively). This also enables simultaneous scanning of two participants (hyperscanning).
- 4D-Neuroimaging (San Diego, USA): Now acquired by CTF systems, the company typically used magnetometers rather than gradiometers. Their system included 248 magnetometer system.

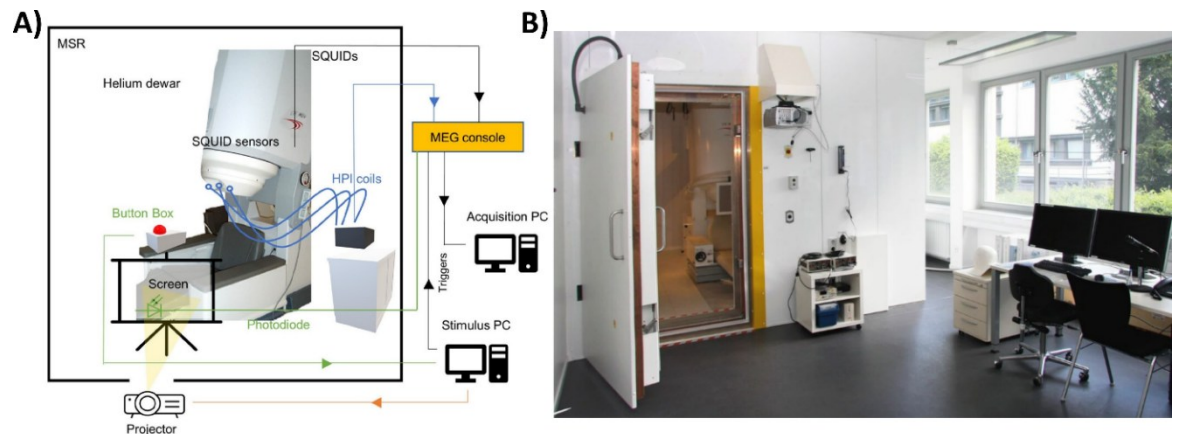


Figure 2.16: A) CTF SQUID-MEG system diagram. Adapted from Rhodes et al., 2023 Picture of a CTF SQUID-MEG system installed at the Brain Imaging Center, Goethe University, Frankfurt. Photo credit to Vacuumschmelze.

These SQUID-based systems operate at extremely low temperatures, typically around 4 Kelvin, requiring liquid helium cooling. While they offer excellent sensitivity and have been the gold standard in MEG for decades, the need for cryogenic cooling presents logistical challenges and ongoing operational costs.

2.2.6 Limitations

SQUID-MEG systems have, for over 4 decades, been the gold standard for MEG neuroscience research. With over 150 systems worldwide, they provide ideal spatial resolution and SNR. Despite their usefulness, these systems come with a number of limitations, mainly introduced by the controlled environment required for SQUID operation. As the example on Figure 2.16B shows, MEG systems require housing inside a magnetically shielded room. MSRs will be covered in detail in Chapter 4, but it is important to note that they can be difficult to site and add significant costs. As we will discuss later, active shielding can alleviate some of the shielding requirements, offering a more flexible solution for on-scalp systems. The cooling of the SQUIDs introduces some additional constraints. The thermal insulation limits the sensor to scalp distance, typically anywhere between 1.5 to 3 cm. Additionally, the SQUID array housed inside the dewar cannot be rearranged, which means the scanner is a one-size-fits-all solution. Scanning participants with varying head sizes can affect data quality, significantly reducing coverage, especially for those with smaller head sizes such as children. Since the fields generated follow the inverse square law, these limitations on the sensor to scalp distance can result in decreased SNR and reduced coverage over certain brain regions. Lastly, the sensor array remains fixed within the central volume of the MSR, normally requiring the participants to be seated and still. This restriction on participant movement makes the study

of motor function or social interactions difficult. The study of certain cohorts can also be affected by this, especially children or people with neurological disorders affecting motor function. Participant comfort is another consideration, as the confined space and requirement for minimal movement can be uncomfortable for some individuals, potentially affecting data quality or limiting study populations.

Chapter 3 Optically pumped magnetometers

This chapter offers a detailed overview of OPMs, with a focus on the physical principles underlying their design and operation. To contextualize OPMs, we first examine alternative technologies showing promise in biomagnetism applications, particularly MEG. We then introduce OPMs, tracing their historical development and subsequent practical applications. The physics sections delve into the working principles of OPMs, specifically exploring how light-matter interactions probe and manipulate atomic energy levels. Our discussion centres on magnetometry techniques employing high-density rubidium vapor cells, which form the core of OPMs manufactured by QuSpin Inc. These sensors were exclusively used in all experimental work presented in this thesis.

3.1 Emerging technologies

SQUID-MEG systems remain the most widely used and validated technology for high-precision neuromagnetic measurements. Regardless, the limitations discussed in the previous chapter have spurred the search for alternative approaches. Several promising alternatives have emerged over the years, which we discuss below.

3.1.1 High Temperature SQUIDS

High-temperature superconducting (HTS) SQUIDS have emerged as a promising technology for on-scalp MEG measurements (Zhang et al., 1993). Unlike their low-temperature counterparts, HTS SQUIDS can operate at temperatures achievable with liquid nitrogen cooling, typically around 77 K (Öisjöen et al., 2012). Compared to the 4 K used for conventional SQUIDS, this higher operating temperature offers several advantages, including reduced thermal insulation requirements and the potential for closer sensor-to-scalp distances. Figure 3.1 shows examples of early experimental work with small numbers of channels, and reported sensor-to-scalp distances as low as 1 mm (Pfeiffer et al., 2019). The development of HTS SQUIDS for MEG applications has been driven by advances in materials science and fabrication techniques. These devices are typically based on yttrium barium copper oxide (YBCO) thin films, which exhibit superconductivity at relatively high temperatures (Faley et al., 2001). The use of simpler cryogenic systems could potentially reduce the overall size and cost of MEG systems.



Figure 3.1: **A)** 7-channel HTS SQUID array in a cryocooler, developed at Chalmers University in Gothenburg. **B)** On-scalp MEG recording system captured at the Swedish National Facility for Magnetoencephalography (NatMEG). Both adapted from Pfeiffer et al., 2019.

One of the key advantages of HTS SQUIDs is the possibility of creating more flexible sensor arrays. The reduced cooling requirements allow for the development of smaller, more modular sensor units that can be positioned closer to the scalp. This closer proximity can help increase signal-to-noise ratios and spatial resolution in MEG measurements (Andersen et al., 2017; Riaz et al., 2017). However, HTS SQUIDs face several challenges that have limited their widespread adoption in MEG systems. The intrinsic noise levels of HTS SQUIDs are generally an order of magnitude higher ($\sim 50 \text{ fT}/\sqrt{\text{Hz}}$ at 10 Hz) than those of low-temperature SQUIDs, which can impact the detection of weak neuromagnetic signals (Öisjöen et al., 2012). Additionally, the fabrication of high-quality, reproducible HTS junctions remains a technical challenge. Despite these challenges, ongoing research continues to improve the performance of HTS SQUIDs for MEG applications. Recent studies have demonstrated the feasibility of using HTS SQUID-based systems for on-scalp MEG measurements, showing promising results in terms of spatial resolution and signal quality (Xie et al., 2017).

3.1.2 Hybrid SQUIDs

In 2016, researchers at Royal Holloway University introduced a novel SQUID variant called the HyQUID™ (Shelly et al., 2016). This device may offer enhanced performance and simplified manufacturing compared to traditional SQUIDs. The key distinction in a HyQUID's design is the use of a normal conductor for the weak link within the superconducting loop, as opposed to the conventional SQUID structure (Petrashov et al., 1995). The HyQUID's field detection mechanism relies on Andreev reflections occurring at the interface between superconducting and normal metal components (Petrashov et al., 2005).

York Instruments Ltd. used this technology to develop the MEGSCAN™, a MEG system based on HyQUIDs. This company held the exclusive rights to utilize the HyQUID technology. The system design used a cryogenic solution provided by Oxford Instruments, employing pulse tube refrigeration to maintain superconductivity. The MEGSCAN™'s dewar design closely resembles that of conventional SQUID-based MEG systems, featuring a fixed sensor array and maintaining a space between the sensors and the subject's head. Despite showing great initial promise, a complete HyQUID MEG system is yet to be built. The need for extremely low operating temperatures below 2 K—even colder than conventional SQUIDs—may have presented additional technical challenges that hindered its implementation.

3.1.3 Nitrogen vacancy centre magnetometry

Nitrogen vacancy (NV) centres in diamond offer a novel approach to magnetometry with potential applications in MEG. These quantum defects, created when a nitrogen atom replaces a carbon atom in the diamond lattice, can be manipulated using lasers and microwaves to create a magnetically sensitive state at room temperature (Rondin et al., 2014). NV centres have demonstrated high spatial resolution in magnetic resonance experiments, enabling spin resonance measurements of proteins and imaging of molecules within single cells (Shi et al., 2015; Wang et al., 2019). Nonetheless, current sensitivities exceeding 100 pT/√Hz are insufficient for practical MEG applications (Dale and Morley, 2017). Additionally, the requirement for a microwave source near the participant's head poses technical challenges. Despite these limitations, ongoing research in NV centre magnetometry may lead to future breakthroughs in on-scalp MEG technology, potentially eliminating the need for a microwave source (Dhungel et al., 2024).

3.1.4 Tunnel magneto-resistive sensors

Tunnel magneto-resistive (TMR) sensors have received some interest in the literature for use in MEG at room temperature. These sensors are based on magnetic tunnel junctions (MTJs) that utilize quantum mechanical effects to detect magnetic field changes through electrical resistance variations. Work by Kanno et al., TMR sensors achieved sensitivity levels of 940 fT/√Hz at 1 Hz and 50 fT/√Hz at 1 kHz through the integration of magnetic flux concentrators and optimized amplifier circuits (Kanno et al., 2022). This approach has some promise since the sensors can be positioned as close as 2.6 mm from the scalp surface. However, low sensitivities and the lack of three-axis detection are technical drawbacks that have kept this technology from developing a widespread use in MEG.

3.2 OPMs: An introduction

At the time of writing, Optically Pumped Magnetometers present the most promising alternative to SQUIDs for magnetoencephalography. The foundations of OPM technology stem from pioneering research into magnetic resonance in alkali vapours. During the 1950s and 1960s, the study of light-matter interactions saw significant advancements, driven by groundbreaking work from physicists such as Nobel Prize winners Alfred Kastler and Hans Dehmelt, as well as Jean Brossel and William Bell, among many other notable researchers in the field (Bell and Bloom, 1957; Dehmelt, 1958; Kastler, 1951). Their work showed that it was possible to manipulate and probe the atomic energy level structure using light of certain frequencies. These results opened new research avenues for applied quantum physics, and, most notably, have led to the development of atomic clocks and magnetometers (Bloom, 1962; Markowitz et al., 1958). When combined with progresses in material science (laser diodes, optical filters, glass cell fabrication, etc), these advancements have enabled the production of miniaturised magnetometers of very high sensitivity. This type of technology has a wide range of applications, including detection of nuclear magnetic resonance, space magnetometry, biomagnetism, geophysical navigation and mapping as well as fundamental science research (Boto et al., 2018; Corsini et al., 2011; Dang et al., 2010; Korth et al., 2016; Rosner et al., 2022; Savukov and Romalis, 2005a; Xia et al., 2006).

OPMs exploit the spin properties of alkali atoms, using optical pumping to create a gas whose opacity to laser light is sensitive to local magnetic fields (Dang et al., 2010). These sensors do not require low temperatures, eliminating the need for cryogenic cooling, and can be placed directly on the scalp. Additionally, the theoretical sensitivity of OPMs surpasses that of SQUIDs, with a bandwidth (0-150 Hz) and dynamic range (± 5 nT) suitable for MEG acquisition (Sander et al., 2012; Shah and Wakai, 2013). Recent miniaturization and commercialization have brought OPMs closer to practical MEG applications, with several studies demonstrating their ability to capture brain signals (Boto et al., 2017; Colombo et al., 2016; Johnson et al., 2010; Kamada et al., 2015; Kim et al., 2014; Xia et al., 2006). Due to these advantages, this thesis aims to demonstrate OPM capabilities for MEG applications.

3.3 The atomic energy level structure

The working principles of OPMs are based on the interaction of atoms with electromagnetic fields. The fundamental phenomena that arise from such interaction can be described with the equation

$$\boldsymbol{\tau} = \boldsymbol{\mu} \times \boldsymbol{B}, \quad [3.1]$$

which states that atoms with a magnetic moment $\boldsymbol{\mu}$ will experience a torque $\boldsymbol{\tau}$ when placed in a magnetic field $\boldsymbol{B}$. By applying light of specific frequencies, atoms can be polarized, which means aligning their magnetic moments. When an ensemble of atoms is polarized in this way, the atomic medium gains a bulk magnetisation, which behaves according to equation 3.1. This bulk magnetisation is sensitive to any external magnetic field and ready to interact with it. Then the atomic medium starts to act like a sort of compass. This interaction leads to the well-known phenomenon of Larmor precession, where the bulk magnetic moment rotates around $\boldsymbol{B}$ at a frequency $\Omega_L = \gamma \boldsymbol{B}$, proportional to the atom's gyromagnetic ratio γ . This precession can be probed by observing the outcoming light. With a carefully designed experimental setup, this technique enables precise optical measurements of Larmor precession, which can be used to infer the magnetic field strength. This type of experiment also allows for extremely accurate determination of atomic energy levels. Probing such light matter interactions requires an understanding of the relationship between an atom's magnetic moment and its possible energy levels. Here, we cover the internal atomic interactions that give rise to the energy level structure.

3.4 Fine structure

For brevity's sake, we will focus our discussion on alkali metals, specifically, on rubidium-87 (^{87}Rb). With a half-life of 48.8×10^9 years, this weakly radioactive isotope is commonly used in magnetometry applications. While optical pumping is also possible in diamagnetic atoms such as mercury, barium, or helium, their distinct energy level structure presents unique challenges. These elements typically require more complex pumping schemes and exhibit slower pumping rates (Budker and Kimball, 2013). Among diamagnetic atoms, helium-4 has emerged as a particularly successful candidate, achieving performance comparable to alkali vapours in practical applications as we will discuss later. The magnetometers used in this thesis employ rubidium, which, like all alkali metals, has a single valence electron. This electron contributes to the atom's total angular momentum $\boldsymbol{F}$ as given by the vector sum:

$$\boldsymbol{F} = \boldsymbol{J} + \boldsymbol{I}, \quad [3.2]$$

where $\boldsymbol{J}$ is the electron's total angular momentum and $\boldsymbol{I}$ is the nuclear angular momentum. The electron's total angular momentum $\boldsymbol{J}$ is equal to the sum of its orbital angular momentum $\boldsymbol{L}$ and its spin $\boldsymbol{S}$:

$$\mathbf{J} = \mathbf{L} + \mathbf{S}. \quad [3.3]$$

These vectors are quantized, and therefore, defined by dimensionless quantum numbers such that

$$|\mathbf{S}| = \hbar\sqrt{s(s+1)}, \text{ for } s \in \left\{\frac{1}{2}\right\}, \quad [3.4]$$

and

$$|\mathbf{L}| = \hbar\sqrt{\ell(\ell+1)}, \text{ for } \ell \in \{0, 1, \dots, n-1\}, \quad [3.5]$$

where $\hbar$ is the reduced Planck's constant ($\hbar = h/2\pi$), n is the principal quantum number (i.e. the electron's energy level), s is the electron's spin quantum number and ℓ is the azimuthal (or orbital) quantum number. All of these quantities determine the atom's angular momentum $\mathbf{F}$, which is proportional to its total magnetic moment as expressed by

$$\boldsymbol{\mu} = g_F \mu_B \mathbf{F}, \quad [3.6]$$

where g_F is the Landé factor dependent on F , and μ_B is the Bohr magneton ($\approx (2\pi\hbar) \cdot 1.4\text{MHz/G}$), which corresponds to the magnetic moment of the electron. If we consider only the valence electron's orbital angular momentum, as is the case in the Bohr model, then the orbital energy levels are described by

$$E \approx \frac{-13.6Z^2}{n^2}, \quad [3.7]$$

where Z is the proton number. The diagram in Figure 3.2 shows an example energy level structure for an alkali atom. Here, we consider the subshells $\ell = 0$ and $\ell = 1$, given by the principal quantum numbers $n = 1$ and $n = 2$.

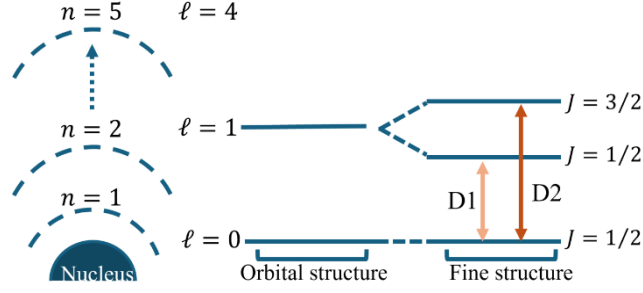


Figure 3.2: Fine structure splitting diagram. Starting with the orbital structure on the left, the electron's spin-orbit interaction leads to splitting of the higher energy level.

In reality, the electron's orbital angular momentum $\mathbf{L}$ creates a magnetic field that interacts with its own spin angular momentum $\mathbf{S}$. From the electron's perspective, the nucleus appears to be moving in a circular orbit around it, creating an effective magnetic field $\mathbf{B}$ that interacts with the electron's intrinsic magnetic moment associated with its spin $\mathbf{S}$. The fine structure splitting occurs because of this spin-orbit interaction, which can be described by introducing relativistic corrections to Schrödinger's equation (Fermi, 1930). Ultimately, this results in an energy difference between the electrons possible orbital states as visualized on the right hand side of Figure 3.2. From equation 3.3, we can see that the electrons total angular momentum number J can only take values that depend on L and S , given by the range

$$|L + S| \geq J \geq |L - S|. \quad [3.8]$$

The valence electron has $s = 1/2$. For every possible value of L we obtain a new set of energy levels. That is, $J = 1/2$ for the ground state, and $J = 1/2$ or $J = 3/2$ for the first excited state.

As shown in Figure 3.2, the energy gap between the fine structure sublevels gives rise to the D1 and D2 transitions, which can be exploited through photon absorption to selectively populate specific energy sublevels. We can estimate the required photon energy with the Planck relation:

$$E = h\nu = \frac{hc}{\lambda}, \quad [3.9]$$

where ν and λ are the photon's frequency and wavelength, respectively, and c is the speed of light. For ^{87}Rb , we can obtain the specific laser wavelengths: 794.98 nm for the D1 transition and 780.24 nm for the D2 transition (Steck, 2003).

3.5 Hyperfine structure

While the electron's spin-orbit interaction gives rise to the fine structure, introducing the nuclear spin reveals additional complexity: each fine structure sublevel hides a number of degenerate states. To obtain a more complete picture, we need to account for the nuclear spin I . Analogous to the case of the electron, the nuclear spin is tied to a nuclear magnetic dipole moment, which interacts with the magnetic and electric field produced by the presence of electrons. Using electromagnetism alone, this system can be described in full, resulting in energy shifts much smaller than those induced by fine structure splitting. Referring back to equation 3.2, we can find a range of possible values for the atom's angular momentum number:

$$|I + J| \geq F \geq |I - J|. \quad [3.10]$$

For atoms with an even-even nucleus, the nuclear spin is zero, whereas for odd numbered nuclei, I takes half-integer values. For our isotope of interest, ^{87}Rb , $I = 3/2$. Using this, we find a new set of energy levels, which is illustrated in Figure 3.3 for the $L = 0$ and $L = 1$ states.

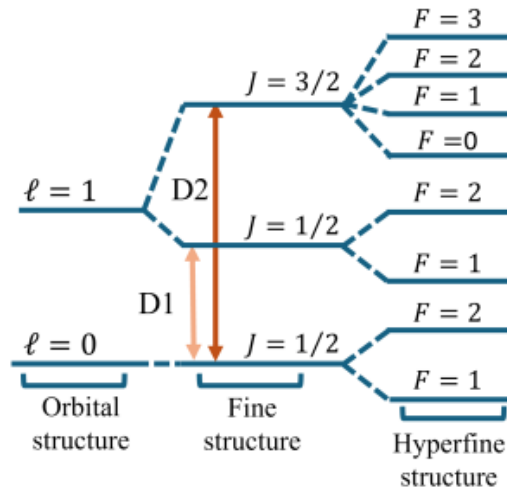


Figure 3.3: Hyperfine structure diagram. Splitting of the fine structure levels occurs due to the nuclear spin interacting with the electron's angular momentum, introducing a new set of levels for every possible value of F .

3.6 Zeeman splitting

Having discussed the hyperfine structure, we now have a more complete picture of what the atomic energy level structure looks like, with ^{87}Rb as our particular example. This, however, can change in the presence of an external

magnetic field. Dutch physicist Peter Zeeman first discovered this phenomenon in 1897, when he observed the splitting of spectral lines of sodium when placed in a 10 kilogauss magnet. This result was later explained by considering the interaction between the external magnetic field $\mathbf{B}$ and the electron's orbital angular momentum $\mathbf{L}$. In essence, if one tries to find a solution for each spherical coordinate $(\mathbf{r}, \theta, \phi)$ in Schrödinger's equation, the solution to the azimuthal equation shows that the z-component of $\mathbf{L}$ must be quantized such that

$$L_z = m_\ell \hbar \quad [3.11]$$

where m_ℓ is known as the magnetic quantum number. Following separation of Schrödinger's equation, the coupling between the equations describing the θ and ϕ components constrain m_l to be integer values equal or less than L . If we describe the system in terms of the atom's total angular momentum, then the atom's magnetic quantum number m_F can only be:

$$m_F = [-F, -F + 1, \dots, F - 1, F]. \quad [3.12]$$

This demonstrates that in the presence of a magnetic field, the hyperfine structure levels, which would otherwise be degenerate, split according to the atom's possible m_F states. For example, the ground state with $l = 0$, $J = 1/2$ and $F = 1$ can contain the Zeeman sublevels $m_F = -1, 0, 1$. As depicted on Figure 3.4, the Zeeman effect splits these otherwise degenerate states into $2J + 1$ equally spaced states. These correspond to different orientations of $\mathbf{L}$ relative to the external magnetic field orientation, with those states opposing the field direction having the highest energies.

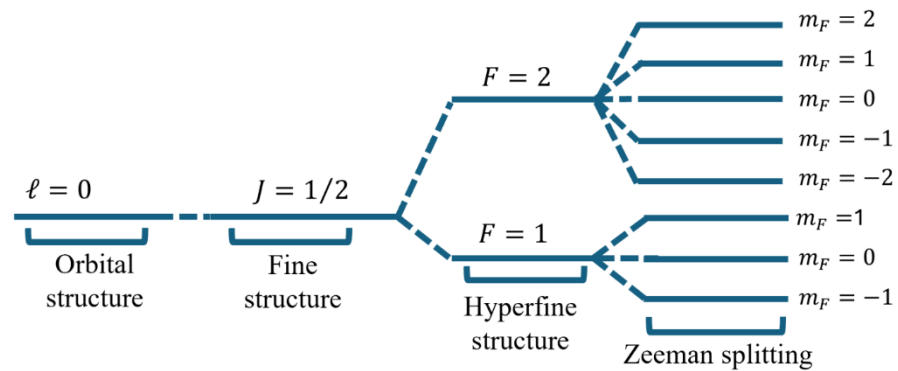


Figure 3.4: Zeeman splitting diagram. Hyperfine structure levels $F = [1, 2]$ split when the atom is exposed to an external magnetic field.

Using the terms discussed previously, the energy difference between these new states is given by

$$\Delta E = m_l \mu_B \mathbf{B}. \quad [3.13]$$

It is important to note this energy difference only applies to the weak-field Zeeman effect, which holds when the atom's internal magnetic field is much larger than the external one ($\mathbf{B}_{ext} \ll \mathbf{B}_{in}$). For larger $\mathbf{B}_{ext}$, the relationship in equation 3.13 becomes non-linear. In such a case, Zeeman shifts are larger than the energy differences introduced by the hyperfine structure. The atom's magnetic moment $\boldsymbol{\mu}$ becomes dependent on $\mathbf{B}_{ext}$, and its time evolution will also be affected by Larmor precession. The energy difference can then be estimated with an expansion:

$$\Delta E = \hbar \Omega = \sum_{n=0}^{\infty} \gamma_n \mathbf{B}^n, \quad [3.14]$$

where Ω is the time evolution frequency of $\boldsymbol{\mu}$, and the coefficients γ_n depend on which states are being mixed due to Zeeman splitting.

As it is normally the case in quantum mechanics, transitions between states are restricted, following a set of selections rules. Transitions between all possible pairs of Zeeman states are not equally likely, with some of them termed as “forbidden” due to their very small probabilities. This is also a consequence of angular momentum conservation and restrictions on the way each quantum number can change. In terms of m_F , the only transitions allowed follow:

$$\Delta m_F = \pm 1, 0. \quad [3.15]$$

This constraint ensures conservation of angular momentum and can also be expressed in terms the uncoupled quantum numbers:

$$\begin{aligned} \Delta \ell &= \pm 1, \\ \Delta m_\ell &= 0, \pm 1, \\ \Delta m_s &= 0, \\ \Delta J &= 0, \pm 1, \end{aligned} \quad [3.16]$$

where m_s is the electron's magnetic quantum number, and the remaining quantum numbers having been defined in equations 3.4, 3.5 and 3.8.

3.7 Optical pumping

Having discussed the atomic energy level structure, we can now explore how this knowledge is leveraged with the technique of optical pumping. This technique consists of selectively populating specific energy levels in atoms by exciting them from lower to higher energy levels using light. This process allows us to leverage the atomic energy level structure, the principle behind OPMs. Here, we focus on the method most relevant to the QuSpin sensors.

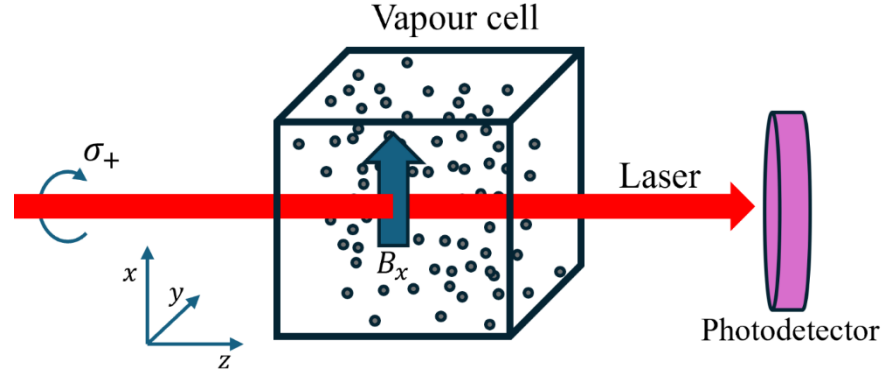


Figure 3.5: Experimental setup diagram for optical magnetometry.

As we have seen previously, transitions between Zeeman sublevels require a change in the atom's angular momentum. This can be achieved via absorption of circularly polarised laser light which results in transitions:

$$\begin{aligned}\sigma_+ \text{ photon} &\rightarrow \Delta m_F = +1, \\ \sigma_- \text{ photon} &\rightarrow \Delta m_F = -1,\end{aligned}\tag{3.17}$$

where σ_+ and σ_- are right and left hand polarisation, respectively. In Figure 3.5 we illustrate the system, with the light propagating through the atomic medium along the z-axis. The polarisation is described using the source as reference, that is, right polarisation σ_+ refers to a clockwise rotation of the light's electric field vector and σ_- corresponds to an anticlockwise rotation. Figure 3.5 depicts a typical setup for optical pumping, where the atoms exposed to the laser are contained in a glass vapour cell.

Using the appropriate wavelength, the atoms absorb the photons and transition to a higher energy level. As we mentioned earlier, a laser wavelength of 795 nm induces the D1 transition in ^{87}Rb ($\ell = 0, J = 1/2 \rightarrow \ell = 1, J' = 1/2$). Following excitation, spontaneous emission of randomly polarised photons then leads to atoms returning to the ground state. If hyperfine levels

were unresolved, this excitation and return to the ground state ($\ell = 1, J = 1/2 \rightarrow \ell = 0, J' = 1/2$) would be a closed transition. However, the presence of hyperfine and Zeeman sublevels means that atoms do not necessarily return to the same ground state sublevel that they started in. This is classed as an “open” transition, and it is one of the main reasons why circularly polarised laser is used in rubidium magnetometers (Auzinsh et al., 2010). By using a circularly polarised laser, the atoms not only undergo the D1 transition but also gain angular momentum. When returning to the ground state, they now have $m_F + 1$, skewing the population to the $m_F = 2$ state. This process is illustrated in Figure 3.6 for atoms being excited from the $F = 1$ and $F = 2$ hyperfine sublevels.

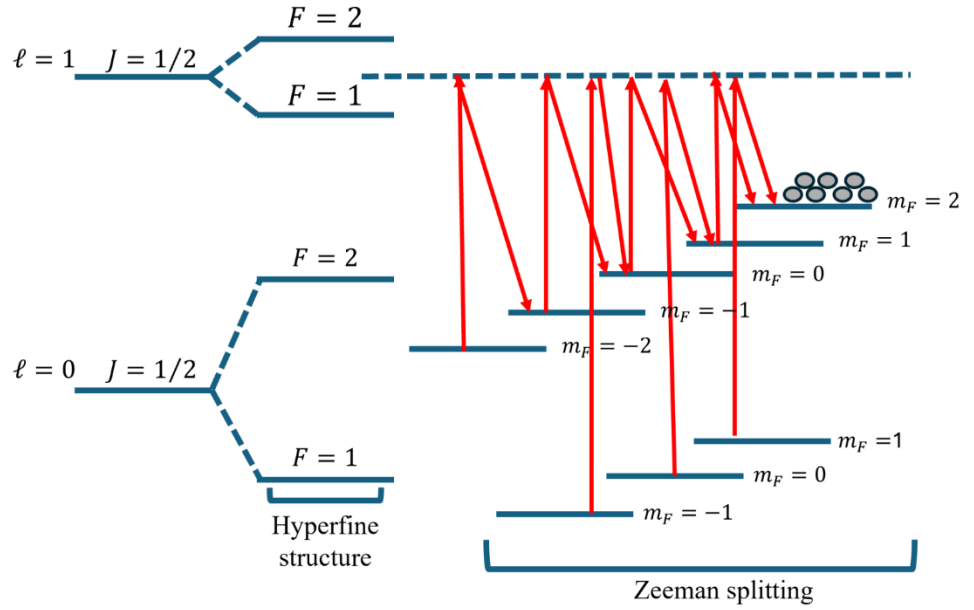


Figure 3.6: Optical pumping process diagram for ^{87}Rb . Following excitation, the atoms return to the ground state having gained angular momentum as indicated by the red arrows. The process is repeated until the atoms can no longer absorb any more photons.

According to the selection rule 3.15, the atoms’ angular momentum may only increase by 1. However, for the $L = 0, F = 2$ state, there are no remaining Zeeman sublevels with higher angular momentum ($m_F > 2$). The system saturates and it now becomes impossible to transfer more angular momentum to the atomic ensemble. These atoms now enter what is known as a “dark” state ($\ell = 0, J = 1/2, F = 2, m_F = 2$), where they cease to interact with the laser light. The time-dependent atomic population distribution among the possible Zeeman sublevels can be described using rate equations. If we consider the 8 Zeeman sublevels of $J = 1/2$, the probability p_k of finding an atom in the k th sublevel is given by

$$\frac{dp_k}{dt} = - \sum_{j=1}^8 (b_{kj} + w_{kj})p_k + \sum_{i=1}^8 (b_{ki} + w_{ki})p_i, \quad [3.18]$$

where b_{kj} is the probability per unit time that an atom has moved from ground state sublevel i to j via photon absorption and re-emission ($\Delta m_F = +1$), and w_{kj} is the probability per unit time that an atom has undergone that same transition via relaxation ($\Delta m_F = -1$) (Franzen and Emslie, 1957). This yields 8 simultaneous equations, which can be solved numerically if one has the coefficients b_{kj} and w_{kj} as shown by Franzen and Emslie, 1957. Simulation results for similar pumping of sodium atoms results are shown in Figure 3.7, which demonstrate how the probability of atoms being in the $m_F = 2$ state (p_8 in the graph) grows following optical pumping compared to the other sublevels. On the other hand, relative light absorption sharply decreases (labelled as β/β_0 in the graph). This redistribution of the population leads to a net bulk magnetisation $\mathbf{M}$, given by

$$\mathbf{M} = \sum_{n=1}^N \mathbf{F}_n \quad [3.19]$$

where N is the number of atoms in the ensemble.

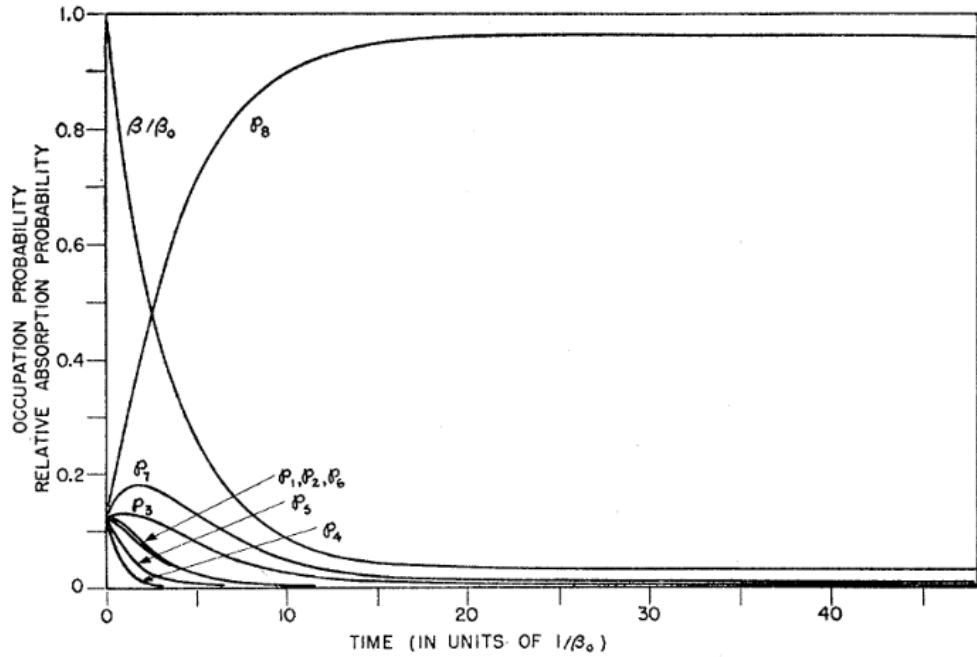


Figure 3.7: Simulation of occupation probabilities for the 8 ground state Zeeman sublevels of a sodium atom. Each line was produced by obtaining a numerical solution to the simultaneous equations 3.18. Curves are labelled in order, from the lowest sublevel to the highest possible one (starting from $F = 1, m_F = -1$ up to $F = 2, m_F = 2$). The line labelled as β/β_0 is the relative

light absorption for each atom per unit time. Note the increase in the excited ground state occupation as the light absorption decreases. Figure adapted from Franzen and Emslie, 1957.

3.8 Spin polarisation and magnetic field interaction

The bulk magnetization vector $\mathbf{M}$ is directly proportional to the atomic polarization vector $\mathbf{P}$, which represents the average atomic spin orientation. In the presence of a magnetic field $\mathbf{B}$, the polarisation vector will evolve in time according to the Bloch equation

$$\frac{d\mathbf{P}}{dt} = \frac{1}{Q(P)} [\gamma \mathbf{P} \times \mathbf{B} - \frac{1}{T} (\mathbf{P} - \mathbf{P}_0)], \quad [3.20]$$

where $Q(P)$ is the nuclear slowing down factor dependent on the polarisation P and T combines the optical pumping rate R and the transverse spin relaxation time T_2 , as given by

$$T = (R + \frac{1}{T_2})^{-1}. \quad [3.21]$$

Following optical pumping, the interaction between the laser beam and the atomic medium is proportional to $(1 - \mathbf{s} \cdot \mathbf{P})$, where $\mathbf{s}$ is the photon spin (Happer, 1972; Shah and Romalis, 2009). The outgoing light therefore contains information about the atomic ensemble, such as the Larmor precession frequency. An analytical solution of the Bloch equation can then be used to infer this information. In our example from Figure 3.5, the laser light propagates along the z axis. Using the steady state solution ($\frac{d\mathbf{P}}{dt} = 0$), we obtain an expression for each component of $\mathbf{P}$:

$$P_x = \frac{\frac{B_y}{\gamma T} + B_x B_z}{\left(\frac{1}{\gamma T}\right)^2 + B_x^2 + B_y^2 + B_z^2} P'_0$$

$$P_y = \frac{-\frac{B_x}{\gamma T} + B_y B_z}{\left(\frac{1}{\gamma T}\right)^2 + B_x^2 + B_y^2 + B_z^2} P'_0 \quad [3.22]$$

$$P_z = \frac{\left(\frac{1}{\gamma T}\right)^2 + B_z^2}{\left(\frac{1}{\gamma T}\right)^2 + B_x^2 + B_y^2 + B_z^2} P'_0$$

where $P'_0 = P_0 RT$. These expressions can be further simplified if we assume that we are only interested in measuring B_x and that B_y and B_z are zero. This gives us:

$$\begin{aligned} P_x &= 0 \\ P_y &= \frac{-\gamma T B_x}{1 + (\gamma T B_x)^2} P'_0 \\ P_z &= \frac{1}{1 + (\gamma T B_x)^2} P'_0. \end{aligned} \tag{3.23}$$

We now have a model of how the polarisation vector will evolve as B_x changes. When plotted with typical values ($1/\gamma T = 30 \text{ nT}$), we obtain the graph shown in Figure 3.8. The P_y component follows a dispersive Lorentzian shape which crosses zero to then reach an asymptote, note the nearly linear behaviour at the zero crossing. The P_z component shows an absorptive Lorentzian peak, with a maximum at P'_0 .

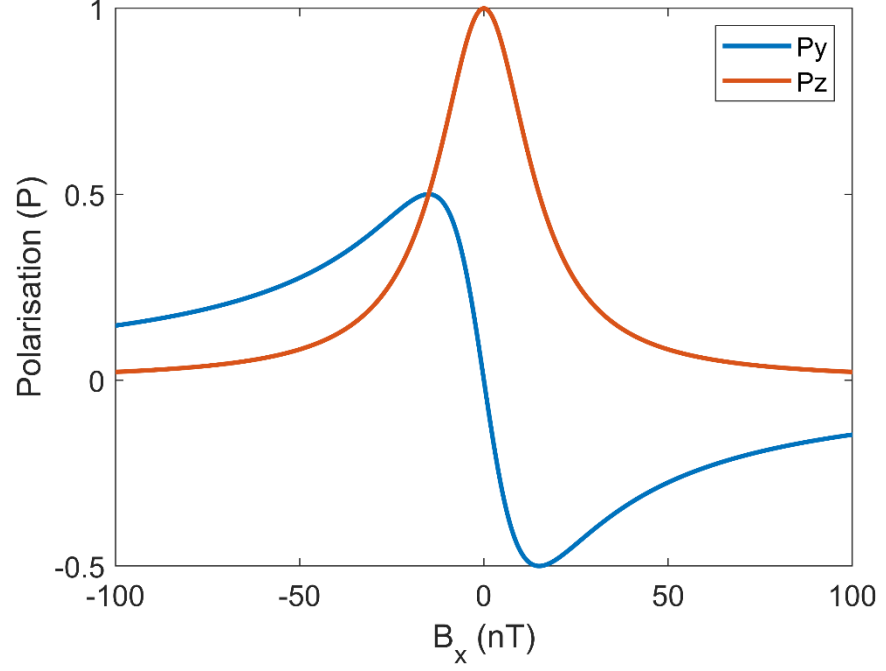


Figure 3.8: Components of the **atomic polarization vector $\mathbf{P}$** as a function of the **applied magnetic field (B_x)** using typical values for a QuSpin sensor ($2/\gamma T = 30$ nT) and assuming B_z and B_y are zero. The plot shows the longitudinal (P_z) and transverse (P_y) components of the polarization, illustrating the characteristic zero-field resonance behavior. The sharp resonance feature near zero field demonstrates the enhanced sensitivity of the atomic system to magnetic field changes in this region.

The behaviour of $\mathbf{P}$ visualised above is known as zero-field resonance. This effect arises from the quantum coherence between Zeeman sublevels in the atomic ground state. As the magnetic field decreases, the energy separation between Zeeman sublevels in the ground state becomes smaller than the natural linewidth of the atomic transitions. This condition allows quantum coherences to develop between previously distinct sublevels, leading to dramatic changes in the optical properties of the atomic vapor. These changes manifest as a sharp resonance feature in both the absorption and dispersion of light passing through the medium. The width of this resonance at half maximum is $2/\gamma T$ for P_z .

3.9 Optical detection

Having established how atomic populations can be manipulated through optical pumping and how these polarised atoms interact with external magnetic fields, we can now discuss how these phenomena enable magnetic field detection. As previously mentioned, the key lies in monitoring changes to the probe light as it passes through the atomic vapor. A semiclassical model of the system can help illustrate how this works (Fabricant et al., 2023). First, the laser can be thought of as a classical electromagnetic field propagating through a medium in which the valence electrons act as oscillating dipoles. The medium is

then said to have a complex index of refraction $n(\omega)$, dependent on the laser's angular frequency ω , as defined by

$$n(\omega) = n_{Re}(\omega) + in_{Im}(\omega). \quad [3.24]$$

This expression relates two distinct phenomena: dispersion and absorption. The real component n_{Re} describes how the medium alters the light's phase velocity (dispersion), while the imaginary component n_{Im} characterizes the attenuation of the light (absorption) (Milonni and Eberly, 2010). Both quantities are dependent on the spin polarisation of the atomic ensemble.

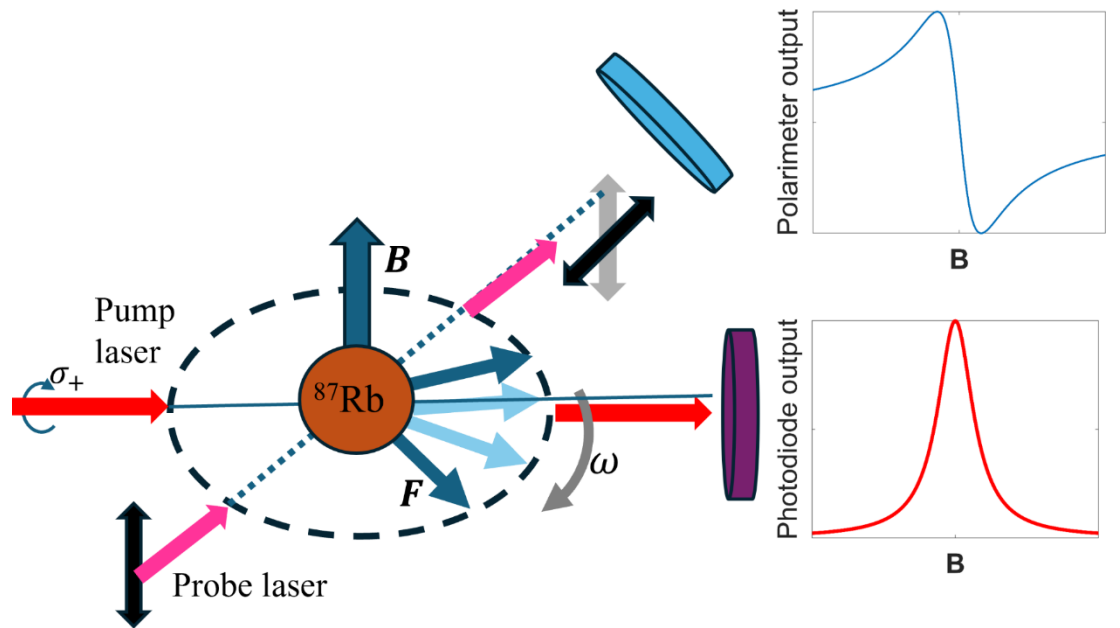


Figure 3.9: Diagram of optical detection of Larmor precession: The diagram illustrates two methods for optical magnetometry. The optical properties of the spin polarised vapour depend on the magnetic field magnitude. This can be probed either by looking at the absorption of a circularly polarised laser, or by measuring the Faraday rotation of a linearly polarised laser.

The relationship in equation 3.24 demonstrates that the same information can be obtained by measuring either the polarisation of the laser or its absorption. The concept is illustrated in Figure 3.9, which shows how one can measure dispersion using linearly polarised light or absorption, by monitoring the pumping laser with a photodiode. Direct laser absorption measurements have proven more practical in some cases, as implemented in QuSpin sensors, which use a single laser beam for pumping and probing. This also greatly reduces the cost of the sensor and makes it easier to miniaturise (Shah et al., 2007; Shah and Romalis, 2009).

3.10 Spin exchange relaxation-free regime

In the example discussed so far, we have ignored the presence of any major relaxation processes. Nevertheless, it is important to consider any factors that may destroy spin coherence, either due to sharp changes in the background magnetic field or internal processes within the atomic ensemble. From Figure 3.8, we can see that a magnetic field increase can destroy spin coherence. QuSpin sensors overcome this issue by countering the background field with a set of coils surrounding the glass cell (Shah and Hughes, 2015). This type of magnetometer is called a zero-field magnetometer, which keeps the atomic ensemble in a low field regime to maintain polarisation and obtain a near linear response to changes in $\mathbf{B}$. For QuSpin sensors this range is normally kept around ± 1.5 nT. In contrast, total field magnetometers do the opposite, measuring the Larmor precession frequency to estimate the total field magnitude.

Presuming the system to be in a low magnetic field regime, the main culprits behind spin-relaxation in atomic magnetometers are spin-exchange collisions and spin-destruction collisions (Budker and Kimball, 2013). These processes influence the fundamental sensitivity limit of an OPM, defined as $\delta\mathbf{B}$. Known as spin projection noise, this limit can be estimated with the general expression

$$\delta\mathbf{B} = \frac{1}{\gamma\sqrt{nT_2Vt}}, \quad [3.25]$$

where γ is the gyromagnetic ratio of the atoms, n is the atomic density, T_2 is again the spin relaxation time transverse to $\mathbf{B}$, V is the glass cell volume, and t is the measurement time (Allred et al., 2002). This expression presents a number of ways in which we may increase sensitivity. Increasing cell volume would help, but this would have its drawbacks like having a lower spatial resolution and having to account for larger numbers of atoms outside of the laser beam. Similarly, increasing measurement time could also help but would reduce our ability to measure fast changing magnetic fields. As we will discuss later, QuSpin sensors address this issue by operating at higher densities (higher n) (Shah and Wakai, 2013).

As we discussed at the start, we are assuming that our atomic ensemble is in a low magnetic field environment (± 5 nT). Under these conditions (high density, low field), spin-exchange collisions start to dominate as the main mechanism for relaxation. This is due to spin-exchange collisions having much larger cross section ($\sim 2 \times 10^{-11}$ cm²) when compared to spin-destruction collisions ($\sim 9 \times 10^{-18}$ cm²) (Allred et al., 2002; Shah et al., 2007). This phenomenon is consistent across multiple alkali atoms, including ⁸⁷Rb, ³⁹K and

^{133}Cs . Additionally, it is common for atomic magnetometers to use a buffer gas, typically a noble gas, which further diminishes the effect of spin-destruction collisions with the walls of the glass cell (Savukov and Romalis, 2005b; Wang et al., 2022). QuSpin sensors use nitrogen as a buffer gas, with a pressure of around 100 torr (Osborne et al., 2018; Shah et al., 2020).

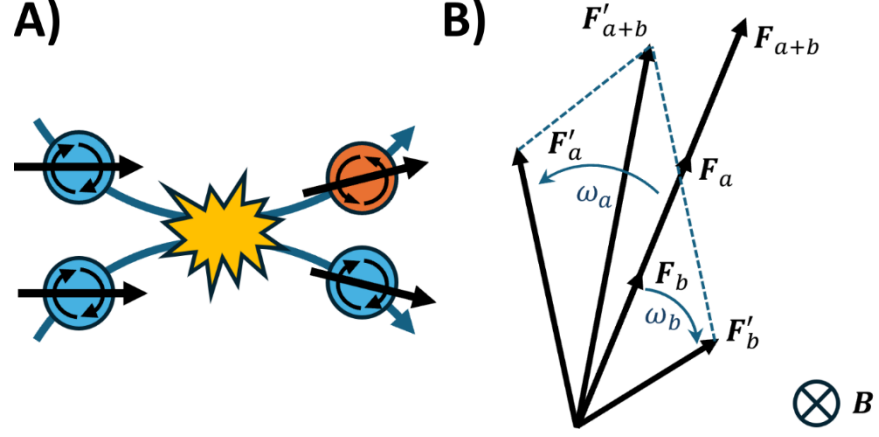


Figure 3.10: Spin-exchange collision diagram: *A)* Depicts spin-exchange collisions between atoms, where the spins of the colliding atoms are exchanged. *B)* Vector diagram showing the angular momentum of two atoms ($\mathbf{F}_a$ and $\mathbf{F}_b$) initially aligned in space, resulting in $\mathbf{F}_{a+b}$. Following a spin-exchange collision, the Larmor precession around a magnetic field $\mathbf{B}$ rotates the two vectors in opposing directions. $\mathbf{F}_a$ becomes $\mathbf{F}'_a$ and $\mathbf{F}_b$ becomes $\mathbf{F}'_b$. The resulting total angular momentum $\mathbf{F}'_{a+b} = \mathbf{F}'_a + \mathbf{F}'_b$ is rotated..

Spin-exchange collisions occur when atoms in the vapour interact during random collisions (see Figure 3.10A). Their electron spins can be exchanged without changing the total angular momentum, causing a randomization of the atomic angular momentum orientations. As illustrated in Figure 3.10B this process reduces the spin polarisation of the atomic ensemble, effectively redistributing populations between the two sets of ground-state hyperfine sublevels $F = I \pm 1/2$ and limiting sensor sensitivity. In this regime, where spin-exchange collisions dominate relaxation, the transverse relaxation time T_2 can be approximated to be:

$$T_2^{-1} \sim T_{SE}^{-1} = n\bar{v}\sigma_{SE}, \quad [3.26]$$

where T_{SE} is the spin-exchange relaxation time, $\bar{v}$ is the relative velocity of the atoms and σ_{SE} is the spin exchange cross section. It then follows that equation 3.25 can be rewritten as

$$\delta\mathbf{B}_{SNI} \approx \frac{1}{\gamma} \sqrt{\frac{\bar{v}\sigma_{SE}}{Vt}}, \quad [3.27]$$

giving us an expression for the fundamental sensitivity of an alkali vapour OPM (Allred et al., 2002). It is important to note that in theory, the sensitivity of OPMs is also affected by quantum fluctuations in the circularly polarise laser (photon shot noise) and the AC Stark effect. These quantum effects are normally considered negligible compared to spin relaxation processes in the literature, especially in practical applications like the one discussed here. A full theoretical treatment by Auzinsh et al., 2004, describes these phenomena, showing that techniques such as spin squeezing can overcome the sensitivity limit.

Although we consider the system to be in a low magnetic field environment, Larmor precession of the atomic magnetic moments is always present. If we consider the two possible hyperfine ground states that the atoms can end up in (either due to pumping or spin-exchange relaxation), the Larmor precession occurs in opposing directions:

$$\omega_{F=I\pm 1/2} = \pm \frac{g_s \mu_B B}{(2I + 1) \hbar}, \quad [3.28]$$

where g_s is the Landé factor for the valence electron. This result shows how spin-exchange collisions can cause decoherence by changing F .

However, something surprising happens if one tries to obtain an analytical solution describing the time evolution of the atom's magnetic moment μ in terms of the electron and nuclear angular momentum ($d\langle S \rangle/dt$ and $d\langle I \rangle/dt$). As shown by Happer and Tang, 1973, for spin exchange rates well below the Larmor frequency ($T_{SE}^{-1} \ll \omega_0$), atomic moments may precess in opposing directions as per equation 3.28. On the other hand, if the spin-exchange rate exchange is greatly increased $T_{SE}^{-1} \gg \omega_0$, then the negative frequency resonance ($\omega_{F=I-1/2}$) spreads over a much larger frequency range, effectively leaving only the positive frequency as a measurable signal. This is known as the spin-exchange free (SERF) regime, and it used in a range of sensors to obtain higher sensitivities (Savukov and Romalis, 2005a; Shah et al., 2007).

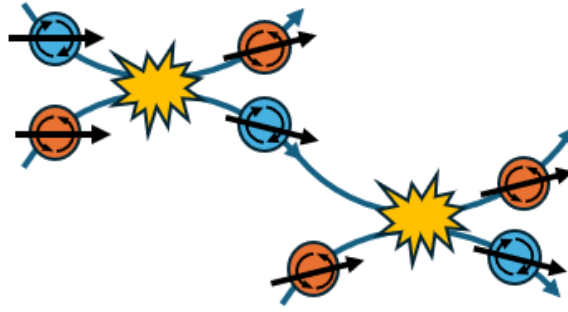


Figure 3.11: Spin-exchange free regime: rapid switching between states due to increased exchange rate leading to a net Larmor precession.

In the case of QuSpin sensors, reaching the SERF regime involves heating of the glass cell to over 150 °C to obtain the desired vapour density. This is done by driving a high frequency voltage through a set of resistive coils which surround the glass cell. Although some research suggests that the fields generated by the heating coils contribute to decoherence of the spins, this is considered to be negligible (Colombo et al., 2016). The voltage frequency used is ~400 kHz, so that it does not interfere with the polarisation process. As depicted in Figure 3.11, the atoms in the SERF regime are switching back and forth between the $F = 1$ and $F = 2$ levels at a higher rate, while still precessing due to the presence of a magnetic field. Since there are more Zeeman sublevels in $F = 2$ than in $F = 1$, the system exhibits a net positive precession due to the imbalance of atom populations between both hyperfine states. This precession occurs at a reduced Larmor precession frequency in this case defined by:

$$\omega_0 = \frac{\gamma^e B}{Q(P)}, \quad [3.29]$$

where γ^e is the gyromagnetic ratio of the electron (Walker and Happer, 1997).

In conclusion, by operating in this regime, SERF-OPMs can reach very high sensitivities, up to 5 fT/ $\sqrt{\text{Hz}}$ (Shah and Romalis, 2009; Tierney et al., 2019; Zhao et al., 2023). While a SERF-OPM presents significant advantages, it is important to remember that the equations described here neglect other aspects of the OPM. Sensitivity is still limited by additional factors including photon shot noise, relaxation due to spin-destruction collision with the walls of the cells, laser amplitude and frequency noise, and various sources of electronic noise.

3.11 Signal equations

Having now discussed all the physical principles that make OPM operation possible, we can now bring together all of these concepts to discuss practical operation of the QuSpin OPM. In Section 3.8, we showed the steady state solution to the Bloch equation describing the behaviour of the polarisation vector that defines the optical properties of the vapour. Performing magnetometry with the setup discussed so far would be possible. However, there are some practical issues to be addressed. First, we have talked about our measurement axis B_x being orthogonal to the direction of the laser beam ($\hat{z}$ axis). This constraint allows B_x to be measured along any direction as long as it is perpendicular to the laser. Therefore, the sensor does not have a defined measurement axis, as changes in both B_x and B_y would induce a measurable response. Additionally, Osborne et al., 2018, demonstrated that such a magnetometer would be highly susceptible to $1/f$ noise. Lastly, it is also important to note that the polarisation along the laser axis is symmetrical around 0 nT, meaning that positive or negative changes in B_x would yield the same measurement. These issues can all be tackled with relatively simple solution: introducing a modulation field B_m along the axis of interest ($\hat{x}$) using a set of Helmholtz coils surrounding the cell (Kastler, 1973). With the addition of this oscillating field, the Bloch equation describing the system now becomes:

$$\frac{d\mathbf{P}}{dt} = \frac{1}{Q(P)} [\gamma \mathbf{P} \times [\mathbf{B} + b_x \sin \omega t \hat{x}] - \frac{1}{T} (\mathbf{P} - P_0 \hat{z})], \quad [3.30]$$

where ω is the modulation field frequency (Cohen-Tannoudji et al., 1970). Solving for this case becomes more complex, as the steady state solution no longer holds. Fortunately a solution exists, as shown by Cohen-Tannoudji et al., 1970, for the case where $B_y = B_z = 0$. The polarisation along the $\hat{z}$ direction is then given by:

$$P_z = \frac{\gamma T B_x}{1 + (\gamma T B_x)^2} J_0 \left(\frac{\gamma b_x}{Q(P)\omega} \right) J_1 \left(\frac{\gamma b_x}{Q(P)\omega} \right) P'_0 \sin \omega t, \quad [3.31]$$

where b_x is the modulation field amplitude and J_n are Bessel functions of the first kind. At this point, using a photodiode or polarimeter to measure the outgoing laser would yield an oscillating signal with a frequency close to ω . Any deviation in the phase of the output signal would suggest the presence of an additional field other than B_x . One could use this phase difference to infer the change in field along $\hat{x}$. This is where the method of phase sensitive detection becomes incredibly valuable.

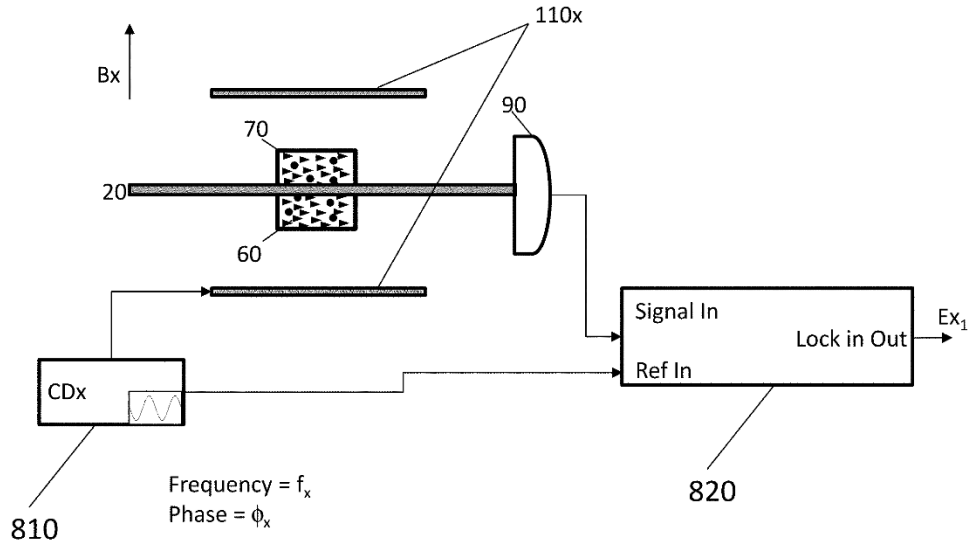


Figure 3.12: Setup used to generate an error signal in the $\hat{x}$ direction. The coil driver (CD) drives the onboard coils by generating a sine wave of frequency f_x and phase Φ_x . This generates a bias field along $\hat{x}$, which modulates the photodiode output. The error signal E_x is obtained by demodulating the photodiode output with a lock-in amplifier using the CD signal as reference. Figure adapted from Shah et al., 2020.

First demonstrated by Slocum and Reilly, 1963, phase sensitive detection has been widely adopted to perform optical magnetometry (Dong et al., 2012; Huang et al., 2016, 2015; Osborne et al., 2018; Schwindt et al., 2007). The setup used to implement this in a QuSpin OPM is illustrated in Figure 3.12. A photodiode produces a voltage signal, which is amplified by a lock-in amplifier (Scofield, 1994). The coil drivers (CD) are connected to both the coils and the lock-in amplifier. The measured photodiode voltage can be demodulated using synchronous phase detection with the lock-in amplifier, with the CD signal as reference. The resulting demodulated output is known in the literature as the error signal (E_x), as it essentially tells us the difference between CD signal and the measured photodiode signal. This is the true output of the QuSpin OPM (Shah et al., 2020). A small change ΔB_x will slightly change the Larmor precession frequency, this will be reflected as a voltage change in the error signal.

We can now use equation 3.31 to find the relationship between the error signal and the field (B_x) transverse to the coils. To avoid confusion, we will simply refer to the error signal as the sensor output V_x . For the sake of simplicity, the Bessel function in 3.31 can be evaluated to a single proportionality constant (A_0). This constant A_0 also incorporates the P'_0 term (Tierney et al., 2019). Lastly, demodulation removes the sine term. As a result, the final form of the equation becomes easier to interpret, with both the Bessel functions and sine terms removed, the output voltage V_x is given by:

$$V_x = \frac{\gamma T B_x}{1 + (\gamma T B_x)^2} A_0. \quad [3.32]$$

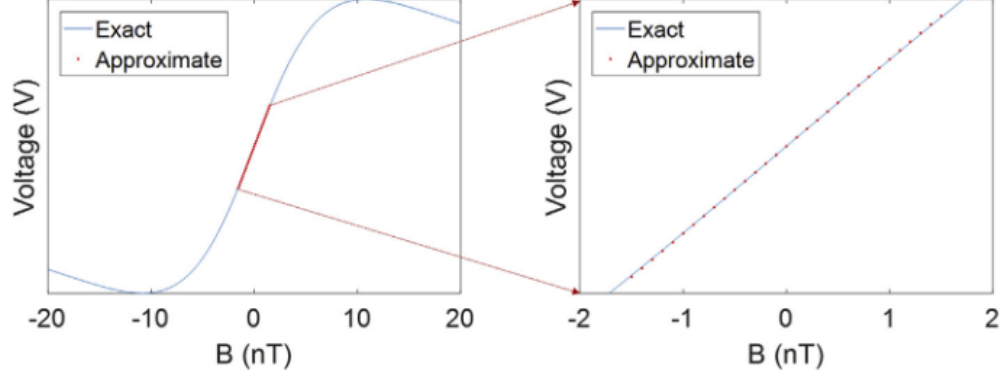


Figure 3.13: Demodulated voltage response over a 40 nT range. A linear fit around the zero-crossing region is shown on the right hand side. This exhibits a less than 1% change from the fit around zero field resonance, for magnetic field values smaller than 2 nT. Figure adapted from Tierney et al., 2019.

The introduction of a modulation field therefore provides a solution to the previously discussed issues. Plotted in Figure 3.13, the voltage measured at the modulation frequency follows a dispersion curve, allowing for distinction between negative and positive magnetic field changes. Additionally, rather than being susceptible to low-frequency dynamics, modulation reveals a clean linear voltage response regime around the zero crossing. In this operational window, defined by the condition $\gamma B_x T \ll 1$, the sensor's output voltage can be approximated using Taylor expansion, giving us

$$V_x = \gamma T B_x A_0, \quad [3.33]$$

which directly tracks the magnetic field strength with a simple proportionality constant $A_0 \gamma T$, known as the sensor gain. The resulting linear correspondence between field and voltage is very valuable for practical applications, with QuSpin devices maintaining this linear behaviour over a ± 5 nT range. As shown by Tierney et al., 2019, we find that a linear fit within the 1 nT range does not deviate more than 1% from the voltage response. Regardless, sharp increases in the magnetic field (± 1.5 nT) result in a non-linear response from the sensor, at which point equation 3.33 no longer applies (Boto et al., 2018). This highlights the need for precise magnetic field control to keep a constant sensor gain (Rea et al., 2021a). Lastly, we now have a clearly defined axis of measurement, determined by the orientation of the sensor onboard coils.

Finding an appropriate modulation frequency for each axis has been a subject of discussion in the literature (Huang et al., 2015; Shah et al., 2020). Additionally, inhomogeneities in the field produced by onboard coils can lead to crosstalk, where the modulation field of one axis inadvertently affects other sensitive axes. To mitigate this issue, researchers typically optimize modulation frequencies and signal phases to minimize inter-axis interference (Nardelli et al., 2019). For instance, in QuSpin sensors, all coils are uniformly driven at 923 Hz with a 90° phase shift; additional parameters such as laser power, cell temperature or modulation depth are tuned during the calibration process.

3.12 Sensor bandwidth

Having described the sensor output and sensitivity in detail, it is also important to consider its frequency response. As stated in Chapter 2, MEG signals can range in frequency from approximately 0.1 Hz to 300 Hz, with the most relevant signals typically concentrated between 1 Hz and 100 Hz. As shown by Allred et al., 2002, the frequency response $s(f)$ of an OPM is equivalent to that of a first-order low pass filter. The response magnitude over a range of frequencies f is then described as the square root of a Lorentzian function:

$$s(f) = \frac{s_0}{\sqrt{1 + (2\pi fT)^2}}, \quad [3.34]$$

where T is again the spin coherence time (or spin relaxation time) (Shah and Wakai, 2013). The fundamental limit on sensor bandwidth is therefore set by T - longer relaxation times allow for higher bandwidth. The spin relaxation time essentially dictates how long we should wait before taking a new independent measurement. From equation 3.33 we can see that increasing T would make for a steeper voltage response, increasing sensitivity. This creates a trade-off between sensitivity and bandwidth. Since sensitivity is also directly proportional to the atoms' relative velocity (equation 3.27) this can be alleviated by increasing the vapour temperature. It is common practice to characterise sensors by their 3 dB bandwidth, which corresponds to the bandwidth where the output signal does not deviate more than 3 dB from its maximum power. The QuSpin sensor has a 3 dB bandwidth of around 150 Hz with spin coherence times of around 1 to 2 ms, well within our frequency range of interest (Shah and Wakai, 2013).

3.13 Cross-Axis projection errors

As shown in Figure 3.13, the linear behaviour of the voltage equation around zero is ideal to measure small changes in the magnetic field as long as the sensing volume is kept within the sensor's dynamic range. It is important to consider, however, that the assumption that the transverse components of the

magnetic field are zero is not practical. Even with the use of passive and active magnetic shielding remnant field will always be present, which means that $B_y = B_z = 0$ is unlikely to be true. Deriving a new solution to equation 3.30 yields:

$$V_x \propto -J_0 \left(\frac{\gamma b_x}{Q(P)\omega} \right) J_1 \left(\frac{\gamma b_x}{Q(P)\omega} \right) \times \frac{\frac{1}{T} \gamma B_x + \gamma^2 J_0^2 \left(\frac{\gamma b_x}{Q(P)\omega} \right) B_y B_z}{\frac{1}{T^2} + \gamma^2 B_x^2 + J_0^2 \left(\frac{\gamma b_x}{Q(P)\omega} \right) \gamma^2 B_y^2 + J_0^2 \left(\frac{\gamma b_x}{Q(P)\omega} \right) \gamma^2 B_z^2} \quad [3.35]$$

This new expression shows that the sensor output for measuring the magnetic field along the x-axis is dependent on the transverse magnetic field components B_y and B_z . Simulation results for increasing magnitudes of B_y and B_z are shown on Figure 3.14. Non-zero values for these transverse components change the slope of the linear region of V_x , effectively introducing error into our measurements by changing the sensors output gain.

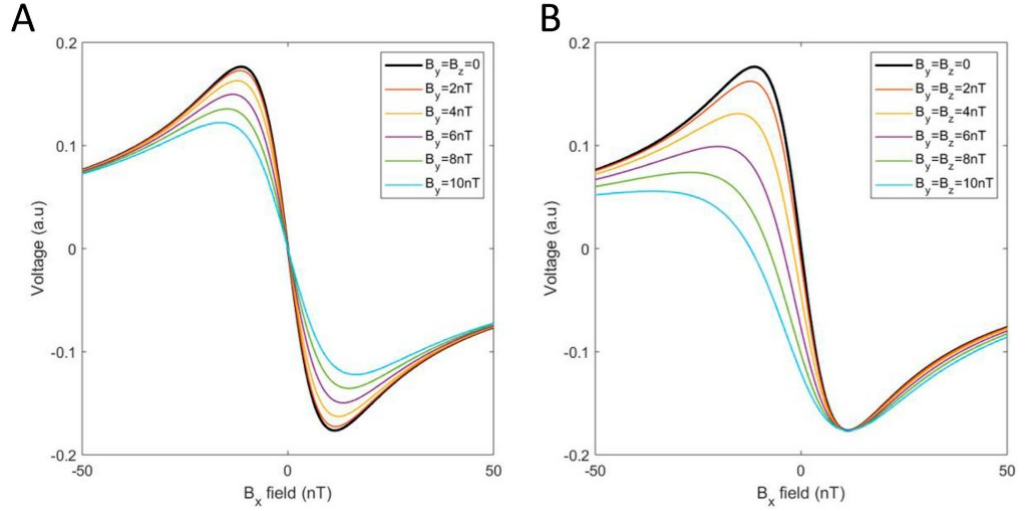


Figure 3.14: Bloch equations solution under different magnetic field conditions: A) Solution incorporating a non-zero transverse magnetic field ($B_y \neq 0$), contrasted with **B)** The solution when both transverse and longitudinal magnetic fields are present ($B_y = B_z \neq 0$), revealing the limitations of the initial simplified case where $B_y = B_z = 0$. Figure adapted from Schofield et al., 2022.

Known as cross-axis projection error (CAPE), this phenomenon has garnered significant attention in the literature due to its impact on OPM performance (Borna et al., 2022; Robinson et al., 2022). Fortunately, there are effective methods to address this problem. The implementation of negative feedback loops offers one solution, this involves using onboard coils to offset fields that could alter the voltage response. Additionally, creating an

environment with extremely low magnetic fields through passive and active magnetic shielding can essentially eliminate CAPEs altogether (Boto et al., 2018). Nonetheless, the influence of CAPEs indicates the critical importance of three-axis sensors in OPM systems (Brookes et al., 2021; Rea et al., 2022). Without three-axis sensing, CAPEs could go undetected and uncorrected, potentially leading to significant measurement biases due to changes in the sensor gain. In addition to that, three axis sensors can also provide the spatial information required for very powerful noise removal techniques (Holmes et al., 2023a).

3.14 Alternative approaches

Over the years new methods have been developed to perform optical magnetometry, this has led to a great range of different types of OPMs. They may differ in atomic species, pumping schemes, light polarisation and many more. While SERF-OPMs using circularly polarized light with rubidium vapor make for highly sensitive sensors several alternative methods offer unique advantages. Modulation-based techniques like M_x and M_z magnetometers use linearly polarized probe light combined with RF field or amplitude modulation, enabling operation in Earth-field environments with reduced heading errors, though typically achieving lower sensitivities than SERF systems (Budker and Kimball, 2013). These approaches often prove more practical for field applications despite their reduced sensitivity, offering robust operation and simpler implementation in array configurations. Light modulation of linearly polarised light can also be used to pump the atoms, as demonstrated by Bell and Bloom, 1961. Other implementations use elliptically polarized light, combining pumping and probing capabilities in simplified optical setups, though maintaining stable polarization states presents its own challenges (Shah and Romalis, 2009).

Alternative atomic species and polarization schemes provide different trade-offs. Helium-4 magnetometers, operating with metastable atoms, offer lower operational temperatures and longer coherence times due to their simpler electronic structure, though they require more complex pumping schemes (Beato et al., 2018; Slocum and Reilly, 1963). This type of OPM has become increasingly popular and has been adapted for use in MEG by Mag4Health, a French based company producing Helium-4 based OPM systems. Caesium based systems, with their larger magnetic moment, operate in different temperature ranges and can provide better spectral resolution (Budker and Kimball, 2013). They are very common in geophysical or defence applications, normally implemented in portable systems. The choice between all of these options ultimately depends on specific application requirements, balancing sensitivity needs against operational constraints like magnetic shielding, temperature control, and system complexity. In the context of MEG, miniaturisation and the ability to operate at room temperature are key, making the rubidium based QuSpin OPMs the ideal tool for studying brain function.

3.15 Commercially available sensors

Although the work carried out in this thesis has exclusively utilised QuSpin OPMs, there are still a few emerging companies producing similar products with potential for MEG applications. These include:

- Fieldline Inc. offers the HEDscan system, which has been used for MEG with arrays of up to 128 single axis rubidium OPMs (Alem et al., 2023). Fieldline sensors have a noise floor of around 15 fT/ $\sqrt{\text{Hz}}$ with a 3 dB bandwidth of up to 200 Hz in a single axis configuration.
- Mag4health produces an OPM-MEG system based on Helium-4 OPMs, which offer a higher bandwidth in exchange for lower sensitivity (noise floor at 25 fT). Their system can house up to 96 tri-axial sensors in a flexible helmet configuration which can adapt to different head sizes.

3.16 The QuSpin triaxial OPM

The experimental work carried out in this thesis utilised an array of QuSpin Zero-Field Magnetometers (QZFM) Gen-3 triaxial sensors. While QuSpin's most popular product remains the QuSpin Total-Field Magnetometer (QTFM), used in geophysical applications, their zero-field magnetometers, designed to operate in low field environments, have proven to be key to the development of OPM-MEG. Shown in details in Figure 3.15A, C and D, their triaxial variant has a noise floor of 15 fT/ $\sqrt{\text{Hz}}$ with a bandwidth of 3-100 Hz. Three axis measurements are achieved with the use of a second laser beam (along $\hat{x}$), perpendicular to the first beam (Figure 3.15B). The initial beam (sensitive in the $\hat{x}$ and $\hat{y}$ directions) is split using a beam splitter. The two resulting beams are then redirected into the glass cell using mirrors, ensuring they are orthogonal. It then follows that the resulting orthogonal beam (along $\hat{x}$) can measure changes in $\hat{z}$ and $\hat{y}$. This means the sensor samples the same atomic ensemble twice, which slightly lowers sensitivity in the other axes. Overlap between the beams can destroy spin coherence, reducing sensitivity. QuSpin effectively eliminated the overlap volume by separating the beams with a gap of $\sim 0.65 \pm 0.25$ mm. The use of buffer gas also helps alleviate this issue, since it limits the atoms from diffusing from one beam to the other while they maintain polarisation (~ 1 ms) (Shah et al., 2020). The resulting sensitivity is 13.5 ± 0.8 fT/ $\sqrt{\text{Hz}}$ in $\hat{x}$, 9.9 ± 1.4 fT/ $\sqrt{\text{Hz}}$ in $\hat{y}$ and 14.9 ± 2.0 fT/ $\sqrt{\text{Hz}}$ in $\hat{z}$ which is still very similar to its dual-axis counterpart with a sensitivity of 11.3 ± 1.5 fT/ $\sqrt{\text{Hz}}$ in $\hat{y}$ and 13.8 ± 1.1 fT/ $\sqrt{\text{Hz}}$ in $\hat{z}$ (Boto et al., 2022).

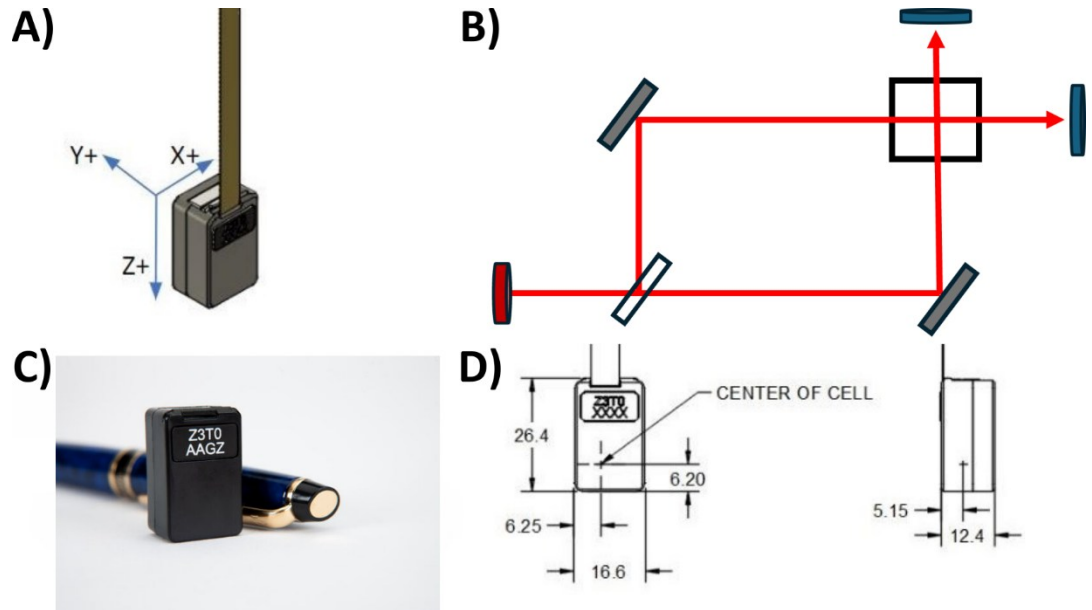


Figure 3.15: The QuSpin Gen-3 QZFM triaxial sensor. Left: A) 3D model showing the X, Y, and Z sensitive measurement axes; C) close-up photograph of the sensor head. Right: B) Schematic diagram showing the laser beam configuration for three-axis measurements; D) Physical dimensions of the sensor head and ribbon cable connector in millimetres.

Three axis sensors present major advantages over single or dual axis designs. As previously discussed, CAPEs can be addressed if one has information about all three axes of the magnetic field, reducing such systematic errors. Additionally, tri-axial sensors provide better coverage over the cortex as demonstrated by Boto et al., 2022. Simulations results are shown on Figure 3.16, highlighting the dramatic increase in coverage. This could also reduce the overall cost of MEG systems, as smaller numbers of sensors can have the same coverage as a bigger array of single or dual axis sensors.

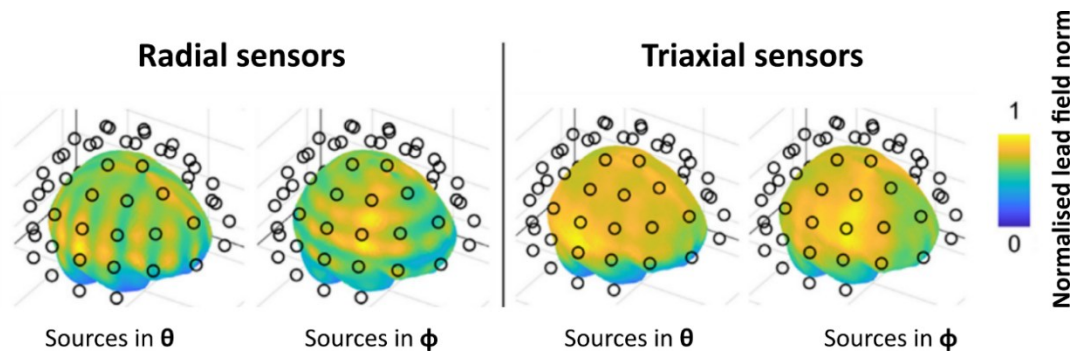


Figure 3.16: Brain coverage simulations. Adult template brain renderings showing coverage as the norm of the lead fields for sources aligned in the θ and ϕ spherical directions. The left-hand panel shows results for single-axis radial sensors and the right-hand panel shows results for triaxial sensors. Figure adapted from Boto et al., 2022.

Figure 3.17A shows the triaxial QZFM package, which includes control electronics, a power supply, cables, and software to interface with the sensor. The control electronics manage both the modulation field and the laser systems, while providing precise temperature regulation for optimal sensor performance. A dedicated digital signal processing board processes the output signals from all three axes, able to implement real-time filtering and signal conditioning. The accompanying software suite enables users to interface with the sensor via USB serial commands. This is used to configure measurement parameters, visualize magnetic field data in real time, and export results for further analysis.



Figure 3.17: QZFM electronics package. Panel A) includes : 1) QZFM sensor head, 2) electronic box, 3) 6.5mm aux cable, 4) 6.5mm BCN splitter cable, 5) micro-USB to USB cable, 6) Shorting cap to protect the sensor head electronics, 7) 19V power supply. **Panel B)** shows the sensor control electronics box. Includes: 1) Power switch, 2) LED sensor status indicators, 3) sensor head connection port, 4) modulation signal outlet, 5) modulation signal inlet, 6) master modulation outlet, 7) Analog signal outlet, 8) micro-USB port, 9) DUNNO, 10) 19V power adapter inlet.

3.17 Field-zero and calibration

In order to start taking measurements, a set of steps are performed to turn on, calibrate and field zero the sensors, as required by the manufacturer. These steps are initiated through serial commands sent by QuSpin's software running on a Windows machine. The device diagram in QuSpin's patent shown on Figure

3.18. The schematics show the glass cell, surrounded by the onboard coils, along with optical path of the laser going through a set of lenses before reaching the photodiode. The photodiode output is amplified and filtered using low noise signal processing electronics. The startup procedure begins by sending a voltage to a set of resistive coils surrounding the glass cell. This rapidly heats up the cell, increasing atomic density until the vapour reaches 150 °C, at which point the SERF regime can occur. Secondly, the laser is switched on and tuned to the D1 transition of ^{87}Rb . At this point, the sensor is turned on and ready to be calibrated.

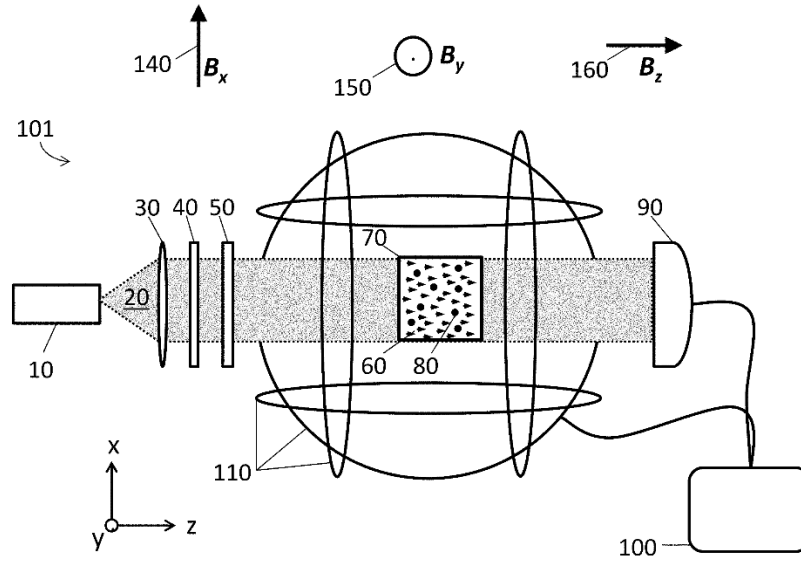


FIG. 1 (PRIOR ART)

Figure 3.18: QuSpin QZFM diagram: Onboard coils surround the glass cell. A set of lenses polarises the and colimates the laser beam. A photoiode measures the laser intensity and the signal is sent to the lock-in amplifier on the electronics control box.

The next step aims to find the parameters required to produce zero field resonance. This can be quite a complex task, as it normally requires knowledge of the background field. This is normally done with an additional non atomic magnetometer such as a fluxgate (Seltzer, 2008; Seltzer and Romalis, 2004). QuSpin implemented a much simpler approach (Shah and Hughes, 2015), which we describe here. If we consider a single axis, for example, axis $\hat{x}$ in Figure 3.15, then a range of values of B_x can be produced using the onboard coils transverse to this axis. The error signal from the lock-in amplifier is monitored over a range of input parameters. These parameters may not only include the voltage to the coils, but also laser tuning values and photodiode amplifying or filtering parameters. The firmware on the control electronics repeats this procedure iteratively for every axis, effectively minimising the width and maximising the height of Lorentzian voltage response from Figure 3.13. The algorithms used for this procedure are normally a type of control loop, such as a proportional-integral-derivative (PID) loop. Once a “field zero” voltage has been found for all three sets of coils, the control electronics will fix the modulation fields to be proportional to this value, effectively countering the background field to induce

zero field resonance. This configuration is known as “open loop”, where the nulling voltages are fixed throughout the measurement process. “Closed loop” configurations continuously update the field zero voltages to counter for field changes that would destroy the linear voltage response. In this case, voltage changes are effectively the magnetometer output. The experimental work carried out in this thesis used an “open loop” configuration, along with active magnetic shielding to ensure appropriate sensor operation.

The last step is the sensor calibration. Briefly put, it aims to obtain a linear response from small changes in $\mathbf{B}$ while minimising crosstalk between the sensitive axes of the sensor. As we will discuss in Chapter 8, this procedure is crucial, as it ensures a fixed sensor output gain and orthogonality between the measurement axes. First, the lock-in amplifier isolates the output signal to the CD modulation frequency. Then, crosstalk between each axis is minimised by tuning the modulation signal parameters iteratively for each axis while monitoring response of the other measurement axes. Once this step is completed, the parameters (such as phase and amplitude) for each modulation field are fixed, and the sensor is ready to acquire data. The output gain can be changed from QuSpin’s interface. Values available are 2.7 V nT^{-1} , 3 V nT^{-1} or 0.33 V nT^{-1} depending on the desired dynamic range for the experiment, exceeding the 1.5 nT range will still results in a nonlinear response if used in open loop mode.

3.18 OPM array for MEG

MEG requires an array of sensors surrounding the participant’s head to simultaneously record the magnetic fields produced by the brain. The closer these sensors are to the brain, the larger the measured signal and the better the data quality, thus an array that can conform to the head shape is favourable. Fortunately, miniaturised, commercial OPMs, such as QuSpin’s QZFM, offer a great deal of flexibility for assembling a multi-channel array that meets these requirements. Their compact form factor and lightweight cabling provide researchers with significant freedom in sensor placement and array configuration.

Early work on OPM-MEG employed bespoke head casts, created using each participant's anatomical MRI scan and manufactured via 3D printing techniques (Boto et al., 2017; Holmes et al., 2018a; Tierney et al., 2018). The casts enabled optimal sensor proximity to the scalp and provided precise information about sensor positions and orientations relative to the participant's head, effectively resolving the co-registration problem. Despite these advantages, this approach is not easily scalable for larger participant cohorts, for which making bespoke casts would quickly become costly and time consuming. Therefore, subsequent iterations have pivoted towards generic rigid helmets designed for specific age groups (Boto et al., 2022; Hill et al., 2020).

This approach has proven to be versatile, with each helmet designed to fit a specific age group based on a set of anatomical MRIs. A template MRI volume is generated from each age group, and the scalp surface is then expanded to obtain the inner surface of the helmet. Figure 3.19 shows a typical setup, with an array of QuSpin triaxial OPMs arranged in a rigid, adult-sized helmet which can hold up to 64 sensors. The sensor slots secure the OPMs near the scalp and are arranged to provide even coverage across the brain. The bulk of the helmet is filled with an inner lattice that significantly reduces the helmet's overall weight making it more comfortable for participants to wear (~650 g when empty, ~900 g with sensors). These helmets, manufactured by Cerca (Nottingham, U.K.), have been successfully produced in multiple sizes to accommodate both adults and children as young as 1 year old. The design has been employed for several research studies, demonstrating its versatility (Boto et al., 2022; Rier et al., 2024; Seedat et al., 2023).

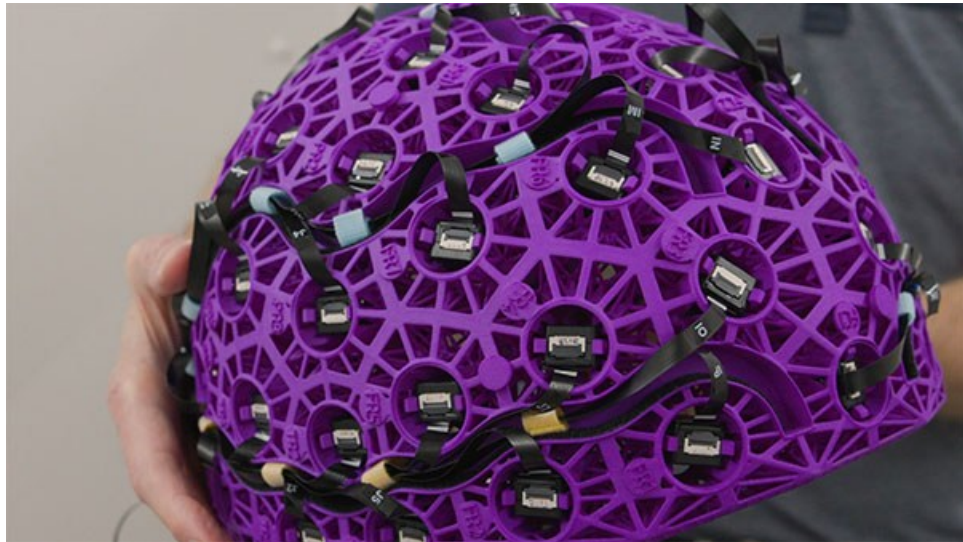


Figure 3.19: OPM-MEG helmet by Cerca Magnetics, Ltd.

The entire experimental setup is illustrated in Figure 1A. Each sensor head in the array is connected to its dedicated electronics box, located outside the MSR, via a 6.5-meter flexible ribbon cable. The electronics boxes are strategically arranged in a server rack to ensure easy access and prevent overheating through careful spacing.

As previously discussed, each sensor requires two distinct signals: one for heating and another for producing the modulation field. While each sensor's electronics box can generate its own modulation signal, this approach can introduce complications. Specifically, small variations in the phase or frequency of individual sensors may create beat frequencies in the sensor output. Two potential solutions exist to address this issue. The first approach involves

deliberately spacing the heating frequencies to ensure that any resulting beat frequencies fall outside the range of interest. However, this method becomes increasingly complex with a growing number of sensors, as identifying heating frequencies that don't induce noise in the 0-100 Hz range becomes challenging. A more practical alternative is to implement a common clock reference. This can be accomplished using an external signal generator or one of the existing electronics boxes. As shown in Figure 2B, this method involves creating a daisy-chain connection between the boxes, utilizing buffer amplifiers to prevent signal degradation. A reference sensor electronics box is selected to share its modulation frequency with all other sensors through this daisy-chain configuration.

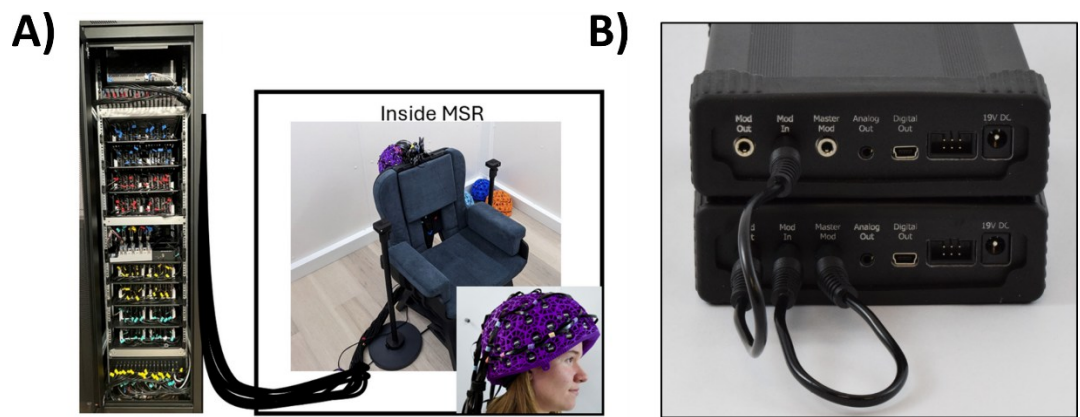


Figure 3.20: *A) Diagram of an OPM-MEG system. Sensor electronics are setup outside the MSR and connected to the sensor array in the helmet. B) Daisy chain setup to share a reference modulation signal between two sensor electronics boxes.*

Chapter 4 Signal processing in MEG

Signal processing plays a crucial role in extracting meaningful information from the complex neurophysiological data acquired in MEG studies. These techniques are essential for enhancing signal quality, reducing noise, and isolating neural activity of interest from the raw MEG recordings. The following sections cover key signal processing methods employed in MEG research, particularly those relevant to the experimental work presented in this thesis. These include preprocessing steps, up to source localisation techniques.

4.1 Filtering and artifact removal

As previously discussed, MEG signals are susceptible to various artifacts, such as eye blinks, muscle activity, and environmental noise. Artifact removal techniques aim to identify and eliminate these unwanted signals from the MEG data, improving the signal-to-noise ratio and facilitating subsequent analysis. Artifact removal techniques, such as Independent Component Analysis (ICA) or Signal Space Separation (SSS), are typically employed to eliminate contamination from eye movements, heartbeats, and external magnetic sources. Such techniques can make a big difference during the data analysis steps as demonstrated in Figure 2.16, which shows artifact rejection results from SQUID-MEG data.

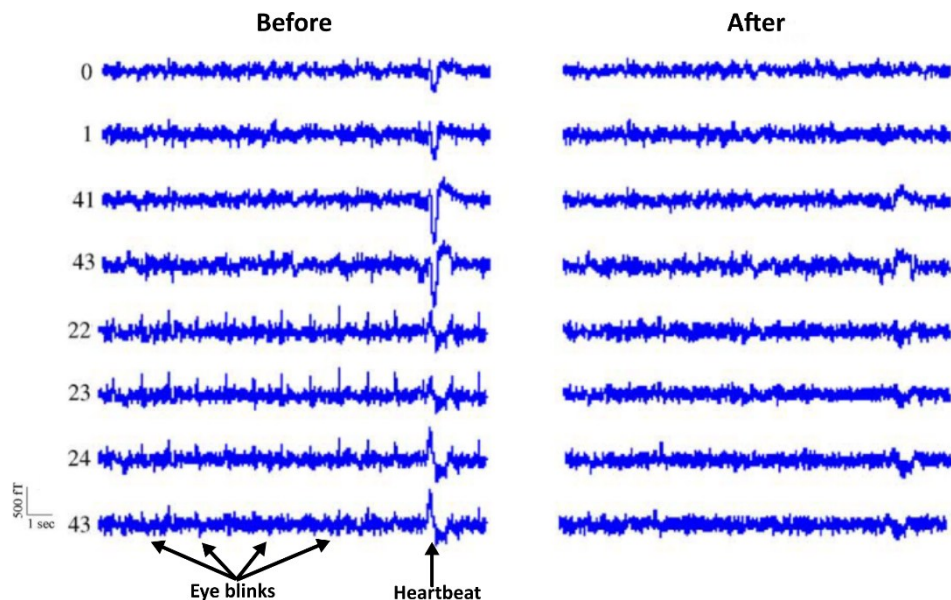


Figure 4.1: Noise-reduced raw MEG signals from channels containing eye blink and heartbeat artifacts before (left) and after (right) artifact removal. Figure adapted from Rong and Contreras-Vidal, 2006.

Frequency filtering is also commonly used to isolate specific bands of interest (e.g., alpha: 8-13 Hz, beta: 13-30 Hz) relevant to the research question. This is usually performed using digital filters in post-processing. A common example is the notch filter, designed to remove a very narrow frequency band, often used to eliminate specific interference sources like power line noise (typically 50 or 60 Hz and their harmonics). Bandpass filters are then used to obtain signals from specific frequency bands.

4.2 Homogeneous field correction

In contrast to cryogenic systems, available OPM-based MEG systems can lack in spatial oversampling, necessitating a simpler approach to model and remove external interference. Tierney et al., 2021, proposed using a first-order spherical harmonic model, effectively treating interference as a constant, homogeneous magnetic field. This method, called homogeneous field correction (HFC), uses the sensors' sensitive axes to model interference. It can be easily implemented in the data processing pipeline. In summary, we define a matrix of unit normals N , which essentially corresponds to our channel orientations in space. From this, the homogeneous field components $\mathbf{B}_{homogeneous}$ can be estimated with

$$\mathbf{B}_{homogeneous} = N^+ \mathbf{B}_{measured} \quad [4.1]$$

where $\mathbf{B}_{measured}$ contains the measured field components and N^+ is the pseudoinverse of N . This background field estimate can then be removed from the data through linear regression.

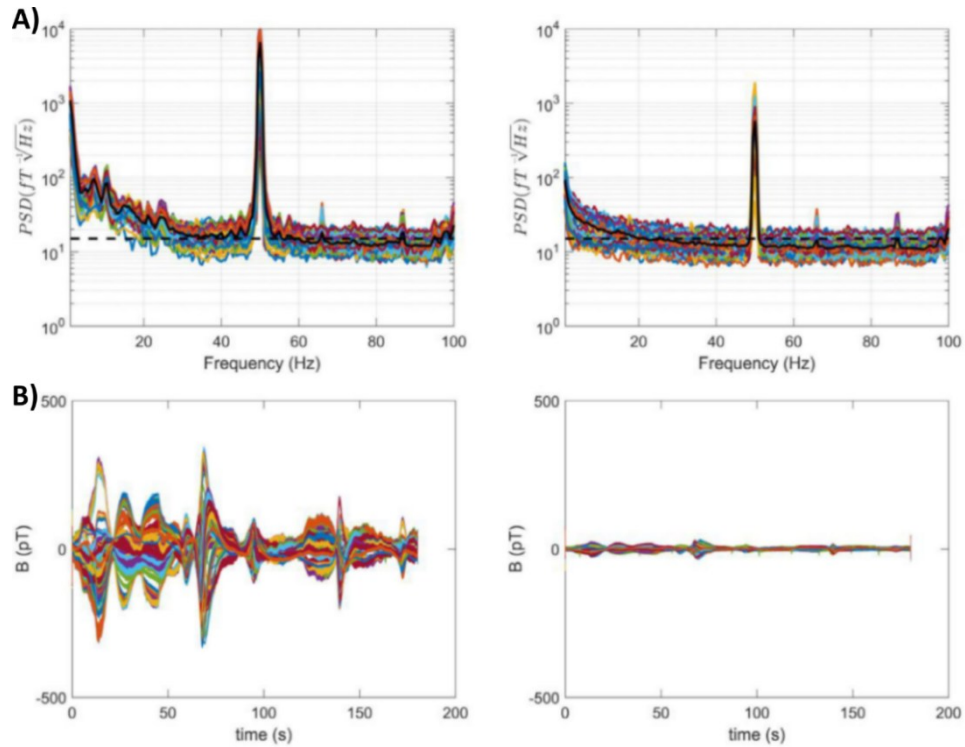


Figure 4.2: Homogeneous field correction for empty room noise: A) Power spectral density and **B)** representative time segments for raw (left) and corrected data (right). Figure adapted from Tierney et al., 2021.

Exemplified with real data in Figure 4.2, HFC can effectively reduce external interference across various frequencies in OPM recordings. An advantage of this approach is its reliance only on sensor orientation, not position, reducing the need for highly accurate sensor calibration compared to higher-order Signal Space Separation (SSS) methods. The simplicity and effectiveness of HFC make it a valuable tool for improving OPM-MEG data quality.

4.3 The inverse problem

Having obtained a set of MEG measurements, researchers ultimately need a way to infer the strength and spatial distribution of neural currents that produced the measured fields. This is known as the inverse problem. This problem is inherently ill-posed (Hadamard, 1902), as there could be an infinite number of current distributions producing the same field pattern. To address this, we can make certain assumptions about the brain. A forward model can be derived, which predicts the magnetic field distribution outside the head from a known brain current source. This well-defined solution, based on Maxwell's equations, forms the foundation for subsequent inverse problem approaches.

4.4 Forward model

As is the case for all electromagnetic phenomena, the fields produced by a current distribution in a volume conductor can be described using Maxwell's equations:

$$\begin{aligned}\nabla \cdot \mathbf{E} &= \frac{\rho}{\epsilon} \\ \nabla \cdot \mathbf{B} &= 0, \\ \nabla \times \mathbf{E} &= -\frac{\partial \mathbf{B}}{\partial t}, \\ \nabla \times \mathbf{B} &= \mu_0 \left(\mathbf{J} + \epsilon \frac{\partial \mathbf{E}}{\partial t} \right),\end{aligned}\tag{4.2}$$

where ϵ is the medium permittivity, μ_0 is the permeability of free space and ρ is the charge density in the medium. As described in Hämäläinen et al., 1993, we can use the quasistatic approximation for these equations since the brain mainly operates in the 1-100 Hz range. This allows us to remove the time varying terms, giving us

$$\begin{aligned}\nabla \times \mathbf{E} &= 0, \\ \nabla \times \mathbf{B} &= \mu_0 \mathbf{J}.\end{aligned}\tag{4.3}$$

If we consider the head to be a volume conductor, with a current density $\mathbf{J}$ at position $\mathbf{r}'(x, y, z)$ and volume G , then we can use the Ampere-Laplace equation to define $\mathbf{B}$ at any position $\mathbf{r}(x, y, z)$ outside the conductor as

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_G \mathbf{J}(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dV'.\tag{4.4}$$

Following from the discussion in Chapter 1, we can decompose the current density into primary ($\mathbf{J}_p$) and volume ($\mathbf{J}_v$) currents such that

$$\mathbf{J}(\mathbf{r}') = \mathbf{J}_p(\mathbf{r}') + \mathbf{J}_v(\mathbf{r}').\tag{4.5}$$

As indicated by Sarvas, 1987, the volume current arises from the interaction between the macroscopic electric field and charge carriers within a conducting medium. Considering Ohm's law, the induced current is proportional to the electric field strength. Assuming the conductivity (σ) of the medium is uniform

throughout, we can express the volume current density $\mathbf{J}_v$ at a given position $\mathbf{r}'$ as $\mathbf{J}_v = -\sigma \nabla V(\mathbf{r}')$, where V is the electric potential. Equation 4.5 thus becomes

$$\mathbf{J}(\mathbf{r}') = \mathbf{J}_p(\mathbf{r}') + -\sigma \nabla V(\mathbf{r}'). \quad [4.6]$$

If we substitute this into equation 4.4, then $\mathbf{B}$ is given by

$$\begin{aligned} \mathbf{B}(\mathbf{r}) = & \frac{\mu_0}{4\pi} \int_G \mathbf{J}_p(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dV' \\ & - \sigma \frac{\mu_0}{4\pi} \int_G \nabla V(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dV'. \end{aligned} \quad [4.7]$$

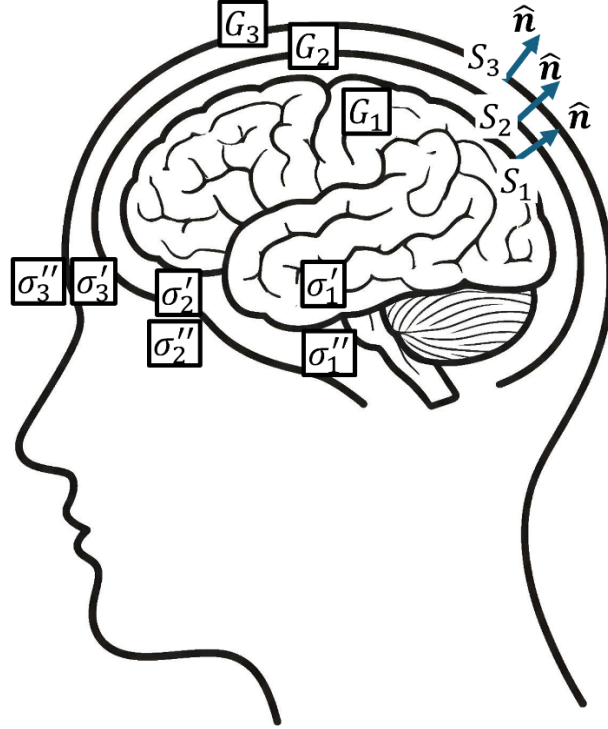


Figure 4.3: Head partition volumes. Diagram showing the compartments used for forward modelling of a human head. Differentiating the brain, skull and scalp with volumes G_j , surfaces S_j and conductivities σ_j .

This last expression shows that the magnetic field produced by the primary current is unaffected by the conductivity of the conductor. If this conductivity profile changes (as is the case in a human head), we can perform the volume integral over a set of n partitions with their own distinct conductivities (σ_j). As depicted on Figure 4.3, these compartments can model the brain, skull and scalp. Introducing this summation of integrals over all partitions for the volume currents yields

$$\begin{aligned} \mathbf{B}(\mathbf{r}) = & \frac{\mu_0}{4\pi} \int_G \mathbf{J}_p(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dV' \\ & - \frac{\mu_0}{4\pi} \sum_{j=1}^n \int_{G_j} \sigma_j \nabla V(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dV'. \end{aligned} \quad [4.8]$$

We can further decompose this expression by using the vector identity $\nabla a \times \nabla b = \nabla \times (a \nabla b)$ on the second term by setting $a = V(\mathbf{r}')$ and $b = |\mathbf{r} - \mathbf{r}'|/|\mathbf{r} - \mathbf{r}'|^3$. If we combine this substitution along with the generalised Stoke's theorem $\int_G \nabla \times \mathbf{X} dV' = \int_S \hat{\mathbf{n}} \times \mathbf{B} dS'$ to replace the Laplace operator, we obtain

$$\begin{aligned} \mathbf{B}(\mathbf{r}) = & \frac{\mu_0}{4\pi} \int_G \mathbf{J}_p(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dV' \\ & - \frac{\mu_0}{4\pi} \sum_{j=1}^n \int_{S_j} \sigma_j V(\mathbf{r}') \cdot \hat{\mathbf{n}}(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dS_j'. \end{aligned} \quad [4.9]$$

This is known as the Geselowitz formula, where S_j' is the surface of volume G_j , and $\hat{\mathbf{n}}(\mathbf{r}')$ is the unit vector perpendicular to that surface at point $\mathbf{r}'$ (Geselowitz, 1970). In this approximation, the volume currents are modelled as a simplified set of currents flowing on each conductive surface S_j . Rather than considering the full three-dimensional distribution of currents throughout the volume, this approach represents them as if they were confined to a two-dimensional surface.

4.5 Single sphere model

Having obtained an expression for the magnetic field that could be measured at a point $\mathbf{r}$ outside the volume conductor, we can now define a geometry that approximates a human head shape. It is quite a common occurrence in physics to model many systems as spheres, and MEG forward modelling is no different. The single sphere model is one of the most common approaches used in MEG analysis (Hämäläinen et al., 1993).

Here, we assume the conducting volume to be bound by a spherical surface S with uniform conductivity σ . For simplicity, we can consider each magnetic field component separately. Since the pickup coils are oriented perpendicularly to the scalp surface, the conventional MEG systems are most sensitive to the radial component $B_r(\mathbf{r}) = \mathbf{B}(\mathbf{r}) \cdot \hat{\mathbf{e}}_r(\mathbf{r})$, where $\hat{\mathbf{e}}_r(\mathbf{r})$ is the radial unit vector at a position $\mathbf{r}$. Introducing $\hat{\mathbf{e}}_r(\mathbf{r})$ into equation 4.9 eliminates the volume currents' contribution since

$$\begin{aligned} \hat{\mathbf{n}}(\mathbf{r}') \times (\mathbf{r} - \mathbf{r}') \cdot \hat{\mathbf{e}}_r(\mathbf{r}) \\ = [\hat{\mathbf{n}}(\mathbf{r}') \times \mathbf{r} - \hat{\mathbf{n}}(\mathbf{r}') \times \mathbf{r}'] \cdot \hat{\mathbf{e}}_r(\mathbf{r}) = 0. \end{aligned} \quad [4.10]$$

This arises from the fact, that since the centre of the sphere is the origin, $\hat{\mathbf{n}}(\mathbf{r}') \parallel \mathbf{r}'$, giving us $\hat{\mathbf{n}}(\mathbf{r}') \times \mathbf{r}' = 0$. Similarly, $(\hat{\mathbf{n}}(\mathbf{r}') \times \mathbf{r}) \cdot \hat{\mathbf{e}}_r(\mathbf{r}) = 0$. This leaves the radial field being defined in terms of the primary current contribution (Sarvas, 1987), so that from equation 4.9 we obtain:

$$B_r(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_G J_p(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \cdot \hat{\mathbf{e}}_r(\mathbf{r}) dV'. \quad [4.11]$$

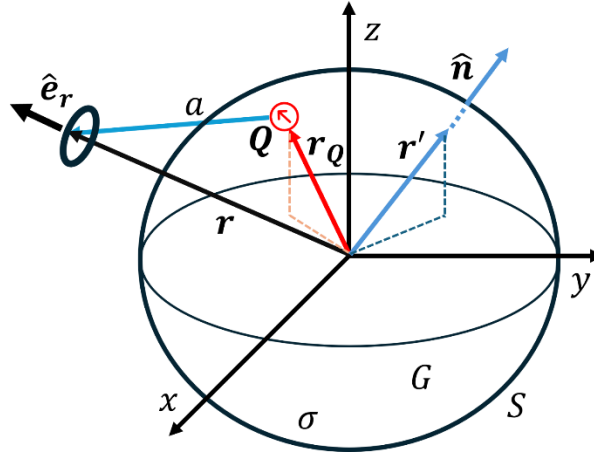


Figure 4.4: Single sphere model diagram. The human head is approximated to be a sphere of volume G with a uniform conductivity σ . Neuronal currents are modelled as a current dipole $\mathbf{Q}$ at a point $\mathbf{r}_Q$. The currents induced by the dipole at all points $\mathbf{r}'$ on the surface are considered to estimate the field at the sensor location $\mathbf{r}$, where $\hat{\mathbf{e}}_r$ is the radial unit vector and $\hat{\mathbf{n}}$ is the unit vector normal to the surface at all points.

The model is described as a diagram in Figure 4.4. Considering the neuronal currents to be a current dipole $\mathbf{Q}$ inside the volume G , at position $\mathbf{r}_Q$. We can then express the current density J_p using the Dirac delta function δ as

$$J_p = \mathbf{Q} \delta(\mathbf{r}' - \mathbf{r}_Q). \quad [4.12]$$

If we substitute this expression into 4.11 and remove the volume currents' term, we obtain

$$B_r(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_G \mathbf{Q} \delta(\mathbf{r}' - \mathbf{r}_Q) \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \cdot \hat{\mathbf{e}}_r(\mathbf{r}) dV'. \quad [4.13]$$

Finally, solving the integral for a single compartment volume with a dipole at $\mathbf{r}' = \mathbf{r}_Q$ yields

$$B_r(\mathbf{r}) = \frac{\mu_0}{4\pi} \mathbf{Q} \times \frac{\mathbf{r} - \mathbf{r}_Q}{|\mathbf{r} - \mathbf{r}_Q|^3} \cdot \widehat{\mathbf{e}}_r(\mathbf{r}). \quad [4.14]$$

It is important to note that this model shows that radial sources (i.e. $\mathbf{Q} \parallel \widehat{\mathbf{e}}_r(\mathbf{r})$) would not contribute to this magnetic field component. Following this, our next task is to develop expressions for the remaining field components. Beyond the boundaries of G , the total current $\mathbf{J}$ becomes zero. This allows us to apply the relationship $\nabla \times \mathbf{B} = \mu_0 \mathbf{J} = \mathbf{0}$. Given these conditions, we can represent the magnetic field using a magnetic scalar potential, which we'll denote as U . This approach simplifies our calculations by reducing the vector field problem to a scalar field problem such that

$$\mathbf{B}(\mathbf{r}) = -\mu_0 \nabla U(\mathbf{r}). \quad [4.15]$$

As shown in Sarvas, 1987, we can find $U(\mathbf{r})$ by solving for an integral of ∇U along a radial line $(\mathbf{r} + t\widehat{\mathbf{e}}_r)$ with limits $0 \leq t \leq \infty$ where $U(\mathbf{r})$ goes to 0 at $t = \infty$. This results in

$$\begin{aligned} U(\mathbf{r}) &= - \int_0^\infty \nabla U(\mathbf{r} + t\widehat{\mathbf{e}}_r) \cdot \widehat{\mathbf{e}}_r dt \\ &= \frac{1}{\mu_0} \int_0^\infty \mathbf{B}(\mathbf{r} + t\widehat{\mathbf{e}}_r) \cdot \widehat{\mathbf{e}}_r dt \\ &= \frac{1}{\mu_0} \int_0^\infty B_r(\mathbf{r} + t\widehat{\mathbf{e}}_r) dt \\ &= \frac{1}{\mu_0} \int_0^\infty \mathbf{B}_Q(\mathbf{r} + t\widehat{\mathbf{e}}_r) \cdot \widehat{\mathbf{e}}_r dt \\ &= \frac{1}{4\pi} \mathbf{Q} \times (\mathbf{r} - \mathbf{r}_Q) \cdot \widehat{\mathbf{e}}_r \int_0^\infty \frac{dt}{|\mathbf{r} + t\widehat{\mathbf{e}}_r - \mathbf{r}_Q|^3}, \end{aligned} \quad [4.16]$$

where we have used equation 4.14 to substitute for B_r . Again, the solution to this remaining integral is given by Sarvas,

$$U(\mathbf{r}) = -\frac{1}{4\pi} \frac{\mathbf{Q} \times \mathbf{r}_Q \cdot \mathbf{r}}{F}, \quad [4.17]$$

where, for simplicity, $F = a(a\mathbf{r} + \mathbf{r}^2 - \mathbf{r}_Q \cdot \mathbf{r})$, $\mathbf{a} = \mathbf{r} - \mathbf{r}_Q$, $a = |\mathbf{a}|$ and $r = |\mathbf{r}|$.

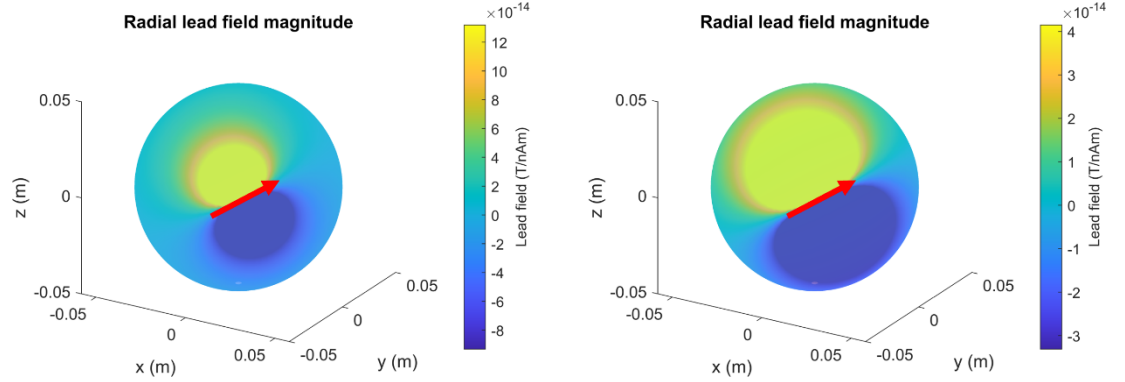


Figure 4.5: Radial magnetic field profiles generated by a tangential 1 nA m dipole within a 5 cm conducting sphere. The left and right panels compare the field distributions for source depths of 1.5 mm and 3 mm, respectively. The colour scales highlight the significant variation in field magnitude due to the change in source depth.

Lastly, we can describe the total magnetic field outside the volume conductor by substituting for the scalar field in equation 4.15, which gives

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi F^2} (F\mathbf{Q} \times \mathbf{r}_Q - \mathbf{Q} \times \mathbf{r}_Q \cdot \mathbf{r} \nabla F), \quad [4.18]$$

where $\nabla F = (r^{-1}a^2 + a^{-1}\mathbf{a} \cdot \mathbf{r} + 2a + 2r) \mathbf{r} - (a + 2r + a^{-1}\mathbf{a} \cdot \mathbf{r}) \mathbf{r}_Q$. This again shows that for a radial source, $\mathbf{B}(\mathbf{r})$ vanishes. Figure 4.5 shows example simulation results for current dipoles placed at different depths. Note the significant difference in the magnitude of the colour bars between the shallow and deeper source locations. This suggests that MEG sensors have higher sensitivity for sources on the cortical surface compared to deeper sources within the brain.

4.6 Single shell model

First introduced by Guido Nolte, 2003, the realistic single shell model offers a more sophisticated approach compared to the single sphere model. This method aims to more accurately represent the complex geometry of the human head while maintaining computational efficiency. Unlike the single sphere model, which approximates the entire head as a perfect sphere, the realistic single shell model uses a single closed surface that more closely follows the actual shape of the inner surface of the skull. This surface is typically derived from individual MRI data, allowing for subject-specific modelling. The mathematical formulation of the realistic single shell model is based on the boundary element method (BEM). First, we need to introduce the concept of lead fields, key in developing these types of models. A lead field $\mathbf{L}$ is a vector field that relates the primary current density in the brain to the magnetic field measured by a sensor at location $\mathbf{r}$. This relationship is given by

$$\mathbf{n} \cdot \mathbf{B}(\mathbf{r}') = \int d^3r \mathbf{J}'(\mathbf{r}) \cdot \mathbf{L}(\mathbf{r}, \mathbf{r}', \mathbf{n}). \quad [4.19]$$

where $\mathbf{L}$ denotes the lead fields, which characterize how a MEG channel responds to a neural current density $\mathbf{J}'$ when oriented in direction $\mathbf{n}$ and positioned at $\mathbf{r}'$. Note that here we follow Nolte's notation, in which he uses $d^3\mathbf{r}$ instead of dV . For practical applications, the brain is normally split into a set of voxels as potential dipole locations. The equation above can then be expressed in a discrete form

$$b_i(t) = \sum_{j=1}^M l_{i,j} \cdot q_j(t), \quad [4.20]$$

where $b_i(t)$ is the field measured by sensor i at time t , for a dipole of strength q in voxel j . As demonstrated in Heller and van Hulsteyn, 1992, for sources oscillating at a frequency ω , we can define the lead field as

$$\mathbf{L}(\mathbf{r}, \mathbf{r}', \mathbf{n}, \omega) = \frac{\mathbf{E}(\mathbf{r}, \mathbf{r}', \mathbf{n}, \omega)}{i\omega} \quad [4.21]$$

where $\mathbf{E}$ is the electric field produced by a unit magnetic dipole with position $\mathbf{r}'$ and direction $\mathbf{n}$. This definition breaks down for MEG, where the quasistatic approximation for Maxwell's equations means that $\omega = 0$. Nolte presents a theorem for the magnetic lead field under such quasistatic conditions for arbitrary conductivity distributions. This is obtained by integrating Biot-Savart's law over a whole, arbitrary volume conductor. This is expressed as a more general form of equation 4.4 which can be applied to any current distribution, including non-closed paths

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int d^3\mathbf{r}' \mathbf{J}(\mathbf{r}') \times \nabla \frac{1}{|\mathbf{r} - \mathbf{r}'|}. \quad [4.22]$$

For simplicity, the term $\mathbf{G}(\mathbf{r}, \mathbf{r}')$ is used to abbreviate the expressions used in the derivation such that:

$$\mathbf{G}(\mathbf{r}, \mathbf{r}') = \frac{\mu_0}{4\pi} \nabla \frac{1}{|\mathbf{r} - \mathbf{r}'|}. \quad [4.23]$$

It is also important to note that for Nolte's derivation of the lead fields, the conductivity σ is described by a rank-two tensor. This captures the directional dependence of conductivity, since a material might conduct electricity better in one direction than another. In practice, the conductivity is typically assumed to be homogeneous, so a scalar value is used. Additionally, the lead field is described by a divergence-part $\mathbf{A}$ and a curl-free part ∇U

$$\mathbf{L} = \mathbf{G} \times \mathbf{n} - \nabla U = \mathbf{A} - \nabla U. \quad [4.24]$$

With these starting points, Nolte is able to solve the integral 4.22 to establish two results. First, we find that the product of the transpose of the conductivity tensor and the lead field results in a divergence-free vector field

$$\nabla \cdot \sigma^T \mathbf{L} = \nabla \cdot \sigma^T (\mathbf{G} \times \mathbf{n} - \nabla U) = 0. \quad [4.25]$$

Secondly, the lead field in any volume conductor can be expressed as the lead field $\mathbf{L}_\infty$ in an infinite, homogeneous, and isotropic medium minus the gradient of a scalar potential function such that

$$\mathbf{L} = \mathbf{L}_\infty - \nabla U. \quad [4.26]$$

Here, the term U encapsulates the influence of the complex conductivity distribution in the arbitrary volume conductor on the lead field. Nolte then aims to generalize the lead field equation to accommodate an arbitrary volume conductor. This means considering a scenario where the conductivity can vary spatially and might even be anisotropic (different conductivities in different directions). The lead field in this general case is denoted by

$$\mathbf{L} = \mathbf{L}_X - \nabla U \quad [4.27]$$

where $\mathbf{L}_X$ represents the lead field matrix in an arbitrary volume conductor. This ultimately shows us that the lead field in a more accurate head model can be expressed as the sum of the lead field for an idealized spherical conductor plus a minor adjustment term

$$\mathbf{L}(\mathbf{r}) = \mathbf{L}_{sph}(\mathbf{r}) - \nabla U(\mathbf{r}), \quad [4.28]$$

where $\mathbf{L}(\mathbf{r})$ is the full lead field for a specific sensor channel. This, however, remains an ideal solution. We find an ill-defined situation for the lead field potential in regions where the conductivity vanishes (i.e., outside a finite volume conductor). This is because the equations don't provide a clear solution for the potential in these regions. To address this, Nolte proposes an alternative derivation that integrates only over the volume conductor itself, yielding surface terms. For a finite volume conductor, boundary conditions must be introduced. By imposing the boundary condition that the normal component of the lead field vanishes at the boundary of the volume conductor and using the expression for the lead field in an infinite homogeneous conductor, most of the surface terms vanish.

Having summarised the lead field derivation, we can now discuss the practical implementation of such a model. The first step, which is independent of the source's location, involves estimating the coefficients of an expansion that represents $U(\mathbf{r})$ from expression 4.28. $U(\mathbf{r})$ is defined as a basis of harmonic functions U_m so that it satisfies the condition that the lead field should be tangential to the surface of the volume conductor. Therefore, the scalar potential function $U(\mathbf{r})$, is given by

$$U(\mathbf{r}) = \sum_{m=1}^M a_m U_m(\mathbf{r}). \quad [4.29]$$

Consider a finite volume conductor with a set of normals $\mathbf{n}_n$ at locations $\mathbf{r}_n$. The coefficients of this expansion are chosen to minimise the error for the boundary condition $\mathbf{n}_n \cdot \mathbf{L}(\mathbf{r}_n) = 0$, which means that the lead field from a dipole on the surface is tangential to the surface. The error is calculated using

$$\sum_n (\mathbf{n}_n \cdot \mathbf{L}_{sph}(\mathbf{r}_n) - \sum_m a_m \mathbf{n}_n \cdot \nabla U_m(\mathbf{r}_n))^2. \quad [4.30]$$

This minimization problem can be solved as a matrix equation if we define a matrix C given by $C_{nm} = \mathbf{n}_n \cdot \nabla U_m(\mathbf{r}_n)$ and a vector $\mathbf{b}$ with elements $b_n = \mathbf{n}_n \cdot \mathbf{L}_{sph}(\mathbf{r}_n)$. The solution for a set of coefficients $\mathbf{a}$ is then given by

$$\mathbf{a} = (C^T C)^{-1} C^T \mathbf{b}, \quad [4.31]$$

which allows us to calculate the lead fields for any given sensor position and orientation.

Once the coefficients are determined in this initialization step, the second step involves calculating the magnetic field for a given dipole source. This is achieved by evaluating the lead field at the source location, which now incorporates the correction obtained from the first step. In a similar way to the single sphere equation 4.14, the magnetic field can then be expressed using the lead field and the dipole moment $\mathbf{Q}$ as

$$\mathbf{n} \cdot \mathbf{B}(\mathbf{r}') = \mathbf{Q} \cdot \mathbf{L}_{sph}(\mathbf{r}_n) - \sum_m a_m \mathbf{Q} \cdot \nabla U_m(\mathbf{r}). \quad [4.32]$$

Figure 4.6B shows an example lead field map for a dipole source placed in the frontal lobe of a template brain. Similarly to the spherical model, deeper

sources will produce weaker extracranial fields. The algorithm's efficiency stems from the fact that the computationally intensive initialization step needs to be performed only once for a given volume conductor and sensor configuration. The subsequent field calculations for different dipole locations are relatively fast, making the algorithm suitable for practical MEG applications where numerous source locations need to be evaluated.

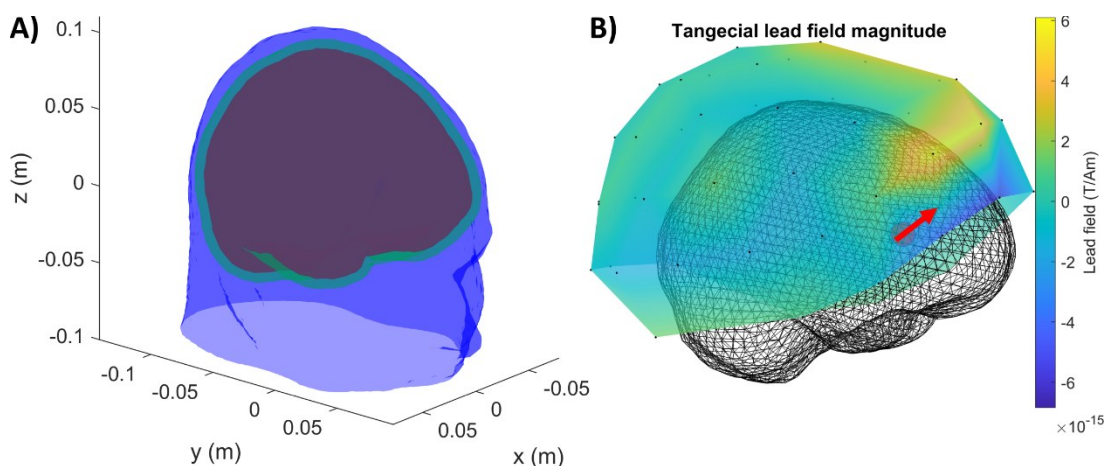


Figure 4.6: **A)** Anatomical MRI template segmentation example, differentiating the scalp (blue), skull (green) and brain (red) surfaces. **B)** Single shell forward model showing the magnitude of the lead fields tangential to the sensor array for a dipole in the superior frontal gyrus. Computed using Nolte's algorithm in MATLAB.

The primary advantage of this model is its improved accuracy in representing head geometry, particularly near the temporal and occipital areas where the spherical approximation is least accurate (see Figure 4.6A). This can lead to more precise source localisation, especially for sources near the cortical surface. However, the realistic single shell model still has limitations. It assumes homogeneous and isotropic conductivity within the shell, which is not entirely accurate for real head tissues. Additionally, it doesn't account for the different conductivities of the brain, skull, and scalp. In MEG analysis, the realistic single shell model is widely used for its balance of accuracy and computational efficiency. It is particularly valuable in studies requiring precise source localisation or when dealing with sources in areas poorly approximated by a sphere.

4.7 Alternative forward models

Over the years, a range of different models have been developed to improve accuracy in MEG source localisation. While the single-shell model presents a good balance of computational efficiency and realistic modelling, researchers may choose different models depending on several criteria. This will depend on the goal of the study itself, the spatial resolution required, access to

computing resources, etc. For example, the multiple sphere model approximates the head using a local, single sphere for each sensor, with each sphere representing different tissue layers with distinct conductivity (Huang et al., 1999). This can account for varying conductivities across the head tissues like the brain, skull, and scalp. The boundary element method (BEM) is another approach that simplifies the complex field equations by assuming the head consists of piecewise homogeneous compartments and reduces the problem to integral equations on the compartment boundaries (Stenroos et al., 2014). As access to increased computing power has become more common, Finite Element Methods (FEM) have gained prominence. They can account for complex head geometries and tissue conductivity variations (Wolters et al., 2006). Unlike spherical models, FEM can incorporate realistic head shapes and represent the skull's inhomogeneous and anisotropic conductivity (Güllmar et al., 2010). This approach discretizes the head volume into small elements, typically tetrahedra, allowing for detailed modelling of different tissue types. Although costly in computational terms, these methods present a good option if spatial resolution is relevant the study. For the experimental work presented in this thesis, we utilised a single shell model for its good spatial resolution but short execution times.

4.8 Beamforming

Beamforming is a powerful spatial filtering technique widely used in MEG data analysis for source localisation and reconstruction (Robinson, 1999; Van Veen et al., 1997). This adaptive method, originally developed for radar and sonar applications (Van Veen and Buckley, 1988), is mainly employed in phased array applications such as telecommunications or medical imaging (e.g. ultrasound scanning). For functional brain imaging, it has been adapted to estimate the contribution of neural sources to the measured MEG signals. As illustrated on Figure 4.7, beamforming works by selectively weighting the sensor outputs to focus on activity from a specific brain location while attenuating interference from other sources. For an array of N sensors, the dipole signal $\hat{\mathbf{q}}_\theta$ with location and orientation θ is defined as

$$\hat{\mathbf{q}}_\theta(t) = \sum_{i=1}^N w_{i,\theta} m_i(t), \quad [4.33]$$

where m_i is the signal measured at a time t , and $w_{i,\theta}$ is the weight for channel i . This formulation is general to most spatial filters, the difference for each particular use case lays in how the weights are calculated.

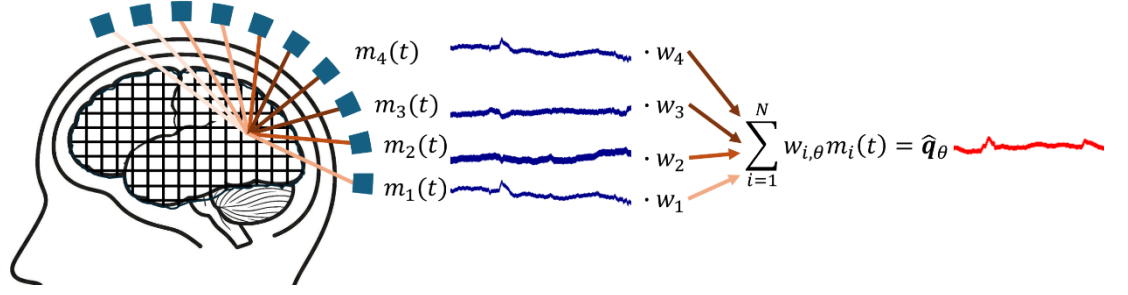


Figure 4.7: Beamforming diagram. The weighted sum of the signals yields a source timecourse for a given source position and orientation, attenuating interference and increasing signal contribution from sensors near the source.

For our use case, we minimize the variance of $\hat{\mathbf{q}}_\theta$ such that the weights pass the signal from the target location and orientation θ with unity gain, while simultaneously minimizing contributions from all other sources. This is expressed mathematically as

$$\min_{\mathbf{w}_\theta} |\langle \hat{\mathbf{q}}_\theta^2(t) \rangle| \text{ subject to } \mathbf{w}_\theta^T \mathbf{l}_\theta = 1, \quad [4.34]$$

where $\mathbf{l}_\theta$ is the lead field for a source position and orientation θ . The forward modelling is calculated for unit dipoles, this means that source power must remain at unity, hence the constraint $\mathbf{w}_\theta^T \mathbf{l}_\theta = 1$. Using these initial conditions, we can now proceed to derive the beamformer weights. First, we substitute the matrix form of equation 4.33 into the expression for the variance and expand out the terms

$$\begin{aligned} \langle \hat{\mathbf{q}}_\theta^2(t) \rangle &= \langle \mathbf{w}_\theta^T \mathbf{m}(t) \rangle \langle \mathbf{w}_\theta^T \mathbf{m}(t) \rangle \\ &= \mathbf{w}_\theta^T \langle \mathbf{m}(t) \mathbf{m}^T(t) \rangle \mathbf{w}_\theta \\ &= \mathbf{w}_\theta^T \mathbf{C} \mathbf{w}_\theta \end{aligned} \quad [4.35]$$

where $\mathbf{C}$ is the covariance matrix between each recorded channel. The elements of this matrix estimated as

$$C_{ij} = \frac{1}{P} \sum_{p=1}^P m_i(t_p) m_j(t_p), \quad [4.36]$$

where P is the number of timepoints recorded. The minimisation problem from equation 4.34 can be solved as a constrained minimisation problem using a Lagrange multiplier λ . If we start with the Lagrangian

$$\mathcal{L}(x, \lambda) = f(x) + \lambda g(x), \quad [4.37]$$

we can find the minimum of the function $f(x)$, given the additional constraint that $g(x) = 0$. Let $f(x) = \langle \hat{q}_\theta^2(t) \rangle$ and

$$g(x) = \mathbf{w}_\theta^T \mathbf{l}_\theta - 1 = 0. \quad [4.38]$$

By substituting these into equation 4.37, we find that the Lagrangian becomes

$$\mathcal{L}(\mathbf{w}_\theta, \lambda) = \mathbf{w}_\theta^T \mathbf{C} \mathbf{w}_\theta + \lambda (\mathbf{w}_\theta^T \mathbf{l}_\theta - 1). \quad [4.39]$$

The partial derivatives of this expression should be zero, so it follows that

$$\frac{\partial \mathcal{L}(\mathbf{w}_\theta, \lambda)}{\partial \mathbf{w}_\theta} = 2\mathbf{C} \mathbf{w}_\theta + \lambda \mathbf{l}_\theta = 0, \quad [4.40]$$

which should be equal to the constraint expressed in equation 4.38, giving us the Lagrange multiplier

$$\lambda = -\frac{2}{\mathbf{l}_\theta^T \mathbf{C}^{-1} \mathbf{l}_\theta}. \quad [4.41]$$

We can then use equation 4.40 to solve for the weights, and this result for λ to obtain

$$\mathbf{w}_\theta^T = \frac{\mathbf{l}_\theta^T \mathbf{C}^{-1}}{\mathbf{l}_\theta^T \mathbf{C}^{-1} \mathbf{l}_\theta}. \quad [4.42]$$

Provided we have calculated the lead fields, we can use this expression to obtain a timecourse for any source position in the brain. In practice, the covariance matrix may be singular or close to singular, which can lead to problems when seeking a unique solution in a system of linear equations. A common approach in MEG signal processing is to regularise the matrix using ridge regression, also known as Tikhonov regularization. The new invertible matrix is defined as

$$\mathbf{C}_r = \mathbf{C} + \mu \mathbf{I}, \quad [4.43]$$

where μ a regularisation parameter and $\mathbf{I}$ is the identity matrix. Parameter μ is normally set to be small percentage to the maximum eigenvalue of $\mathbf{C}$, typically around 5% (Brookes et al., 2008).

Unlike dipole fitting methods, beamforming does not require a priori assumptions about the number of active sources, making it particularly useful for analysing complex cognitive processes involving distributed neural networks. The source space analysis presented in Chapter 5 was performed using

the scalar variant of this type of beamforming. Vector beamformers consider all possible source orientations, while scalar beamformers use a fixed source orientation or aim to find the orientation that yields the highest power output from the source. The beamformer algorithm's ability to suppress external noise and its flexibility in handling time series data have made it a popular choice for both evoked and induced brain activity studies in MEG research.

4.9 Other approaches

The effectiveness of beamforming relies on the assumption that the signals of interest are distinguishable from the background noise based on their spatial and temporal characteristics. In the case of in-phase sources, where multiple sources generate signals with similar or identical time courses, beamforming faces challenges in separating their contributions. Thus, other source localisation techniques are often used, each with its own strengths and weaknesses. For example, minimum norm estimates (MNE) provide a distributed source solution by minimizing the overall source power while explaining the measured magnetic fields. This approach tends to produce smooth and widespread source distributions, which can be useful for identifying broad areas of brain activity but may lack spatial precision. In contrast, dipole fitting methods model the neural sources as a small number of equivalent current dipoles, offering high spatial resolution but potentially oversimplifying the underlying neural activity. The choice between these techniques depends on the specific research question and the nature of the brain activity under investigation. If the goal is to identify focal sources with high spatial accuracy, dipole fitting might be preferred. However, if the brain activity is expected to be distributed or if a more comprehensive picture of the neural dynamics is desired, MNE might be a more suitable choice. Additionally, noise background levels can also be an important factor. This can affect the quality of the data and worsen the source reconstruction results. It is therefore important to choose carefully, since some methods like MNE and beamforming rely on good data quality while others might be more resilient to noise.

4.10 Source space analysis

Moving from sensor level to source space is not the end of story. Most source reconstruction techniques generate timecourses for each potential dipole in the brain. This is what makes such a powerful tool for studying neural activity. These reconstructed signals offer a wealth of information, starting with the precise localisation of brain regions active during specific tasks. Beyond localisation, these signals enable connectivity analyses, providing valuable insights into how functionally distinct brain areas form networks and interact. This capability to map both the spatial and temporal dynamics of neural activity positions MEG as an invaluable method for unravelling the complexities of brain

function. Here we discuss some of the tools available, specifically those commonly used in both SQUID and OPM MEG analysis.

4.10.1 Source signal envelope

For analysing oscillatory activity, the Hilbert transform is often used to extract the envelope of band-limited signals, providing a measure of instantaneous amplitude. To calculate this, we start with the analytic signal for a given a source signal $\hat{q}(t)$:

$$\hat{z}(t) = \hat{q}(t) + iH[\hat{q}(t)], \quad [4.44]$$

where H is the Hilbert transform. This is computed using the Cauchy principal value P of the convolution of $\hat{q}(t)$ with the function $h(t) = \frac{1}{\pi t}$ over the whole signal. In its analytical form, this is given by

$$H[\hat{q}(t)] = \frac{1}{\pi} P \int_{-\infty}^{\infty} \frac{\hat{q}(\tau)}{t - \tau} d\tau. \quad [4.45]$$

From this definition, we can obtain the amplitude envelope of our signals with

$$E[\hat{q}(t)] = \sqrt{(\hat{q}(t))^2 + (H[\hat{q}(t)])^2}. \quad [4.46]$$

This is a very useful tool, since the transform extracts the instantaneous amplitude and phase of neural signals, allowing researchers to examine how neural oscillations in specific frequency bands are modulated during various cognitive tasks. Additionally, it facilitates the calculation of connectivity measures between brain regions. Two common examples are Amplitude Envelope Correlation (AEC), which assesses the similarity in amplitude fluctuations between different brain areas, and Phase Difference Derivative (PDD), which quantifies the rate of change in phase differences between signals from different brain regions.

4.10.2 Source localisation

Contrary to our previous assumptions, the exact position and orientation of neural sources are unknown. To address this, we can determine the source orientation by maximizing the signal-to-noise ratio (SNR) at each potential

location. There is a wide range of source localisation techniques for MEG. Here, we briefly discuss the ones typically used with LCMV beamforming.

Because radial sources generate smaller signals in MEG, we can restrict dipole orientations to the azimuthal plane relative to the head's surface. For each location $\mathbf{r}$, we compute beamformer weights across a range of azimuthal angles ($0 < \varphi < \pi$). We then evaluate the SNR using a pseudo-Z statistic, selecting the angle φ that yields the highest Z value. This value is given by

$$Z_{\mathbf{r},\varphi} = \frac{\mathbf{w}_{\mathbf{r},\theta}^T \mathbf{C} \mathbf{w}_{\mathbf{r},\varphi}^T}{\mathbf{w}_{\mathbf{r},\theta}^T \mathbf{I} \mathbf{w}_{\mathbf{r},\varphi}^T}, \quad [4.47]$$

where we approximate the noise with the identity matrix $\mathbf{I}$. We iterate this process across all brain voxels, generating a volumetric map of Z-scores. By superimposing this functional map onto an anatomical MRI, we can create a comprehensive visualization of brain activity. This can be used to identify which brain regions are engaged during specific tasks. This approach differs from traditional Z-scores, which measure deviation from the mean in standard deviation units. Instead, this pseudo-Z-score provides a measure of signal strength relative to background noise, enabling effective source localisation and activity mapping (Vrba and Robinson, 2001).

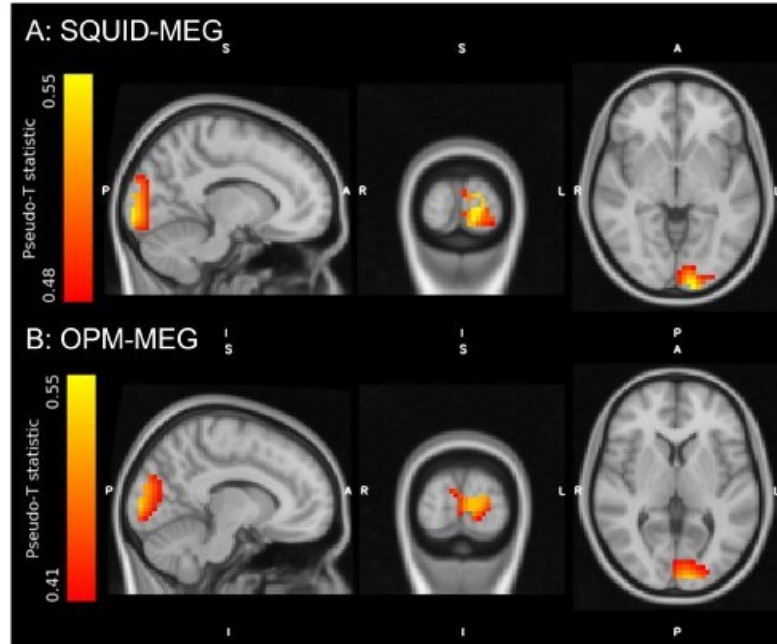


Figure 4.8: Topographical maps displaying regions exhibiting highest theta band power, represented by pseudo-T values and averaged across all participants. Results obtained with both **A)** SQUID-MEG and **B)** OPM-MEG systems. Figure adapted from Rhodes et al., 2023.

Similarly, a pseudo-F statistic measure can also be used to localise sources that alter their activity during time intervals of interest (Vrba and Robinson, 2001). Figure 4.8 shows example results using this technique, being able to accurately localize theta band modulation changes. First, we define the power during an active time window as $Q_a = \mathbf{w}^T \mathbf{C}_a \mathbf{w}$ and similarly, $Q_c = \mathbf{w}^T \mathbf{C}_c \mathbf{w}$ for the control window. From this, the pseudo-F statistic is defined as

$$F = \frac{Q_a - Q_c}{2Q_c}. \quad [4.48]$$

Like the volumetric map of Z-scores, this definition can be applied iteratively to each brain voxel to obtain a volumetric functional image during time windows of interest. Lastly, it is important to note that all source localisation techniques, including the beamforming, rely on accurate knowledge of the sensor locations and orientations relative to the participant's head. The process of obtaining this information is known as co-registration, details about the procedure are discussed in the experimental chapters.

4.10.3 Brain parcellation

The signal processing steps described above yield dipole signals for any potential source position within the volume of the brain. These source positions are defined as the voxels from a structural MRI. For this, researchers normally use each individual's MRI scan to process the data, but generic templates can yield similar results. For high resolution MRI scans ($\sim 1\text{-}2$ mm), this means having hundreds of thousands of source positions. However, rather than focusing on this high resolution picture, many studies prioritize understanding the interactions between broader brain regions and specific tasks, or the interplay among these regions themselves. For instance, the occipital lobe is primarily associated with visual processing, while the postcentral gyrus is key in registering sensory information. Dividing the cortex into larger regions substantially reduces the computational demands compared to voxel-to-voxel calculations. This approach becomes particularly significant when conducting functional connectivity analyses. Consequently, developing consistent methods for partitioning the brain into functionally relevant parcellations is essential for efficient and meaningful MEG data interpretation.

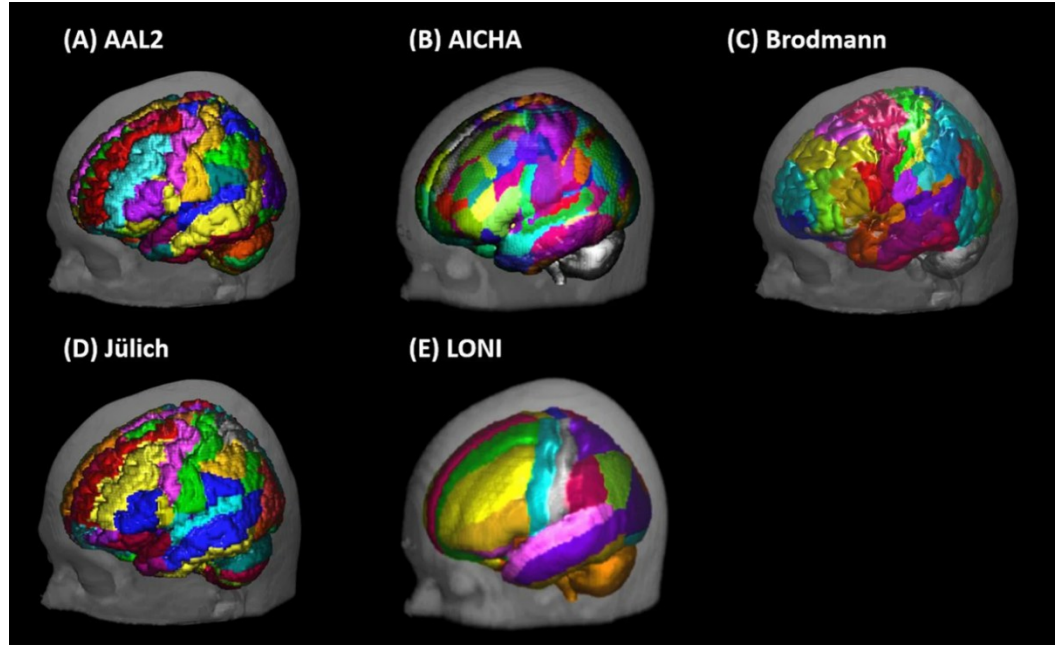


Figure 4.9: Five major brain segmentation maps available overlaid onto a template MRI: **A)** AAL2 (Automated Anatomical Labelling, version 2, **B)** AICHA (Atlas of Intrinsic Connectivity of Homotopic Areas), **C)** Brodmann's areas, **D)** Jülich atlas from SPM Anatomy Toolbox, and **E)** LPBA40 (LONI Probabilistic Brain Atlas). Figure adapted from (Zimeo Morais et al., 2018).

There are various brain templates available for researchers to use for data processing. Some of these are shown in Figure 4.9, highlighting the differences in parcellation between functionally distinct regions. The MNI152 stands out as arguably the most renowned and widely used. This template, developed by the Montreal Neurological Institute for the International Consortium for Brain Mapping (ICBM), represents an average of structural MRI scans from 152 healthy young adults (Mazziotta et al., 2001). The typical procedure involves warping each participant's brain to the standard space and then perform the parcellation. This is how the Automated Anatomical Labelling (AAL) atlas was created (Tzourio-Mazoyer et al., 2002), which serves as the primary parcellation method employed in this thesis (see Figure 4.9A).

4.10.4 Signal leakage correction

A common issue in MEG source space analysis is signal leakage, where activity from one neural source can be mistakenly attributed to another. Other methods also have this problem due to the nature of the inverse problem in MEG. As a result, neighbouring dipoles may exhibit high correlations and abnormal connectivity values, obscuring underlying neural activity (Schoffelen and Gross, 2009). Consequently, researchers have developed a number of methods to alleviate this (Brookes et al., 2012; O'Neill et al., 2015). These normally involve regressing the signal of a region of interest (ROI) from every other possible region assuming there is no time delay between them. This is performed

iteratively across all possible region pairs. Another notable approach is symmetric signal orthogonalization (Löwdin, 1950). First introduced to the field of MEG by Colclough et al., 2015, this method seeks to modify the entire set of reconstructed time-courses, making them orthogonal to each other.

4.11 Bursting

Bursting, characterized by brief periods of high-frequency neural oscillations interspersed with periods of quiescence, has been a topic of growing interest in electrophysiology, including MEG and EEG research. While the precise definition and duration of bursts can vary, these transient events are typically observed across a range of frequencies and brain regions. In recent years, burst analysis has emerged as a valuable approach for examining single-trial dynamics in MEG studies (Jones, 2016; Quinn et al., 2019; Seedat et al., 2020; van Ede et al., 2018). Traditionally, MEG analysis relied heavily on averaging across numerous trials to reduce noise and identify robust phenomena such as evoked responses. While effective, this method often obscured the underlying dynamics of individual trials that collectively produce well-known effects like the beta rebound (Little et al., 2019; Sherman et al., 2016; Shin et al., 2017). Burst analysis addresses this limitation by focusing on the moment-to-moment fluctuations within single trials, offering a more nuanced understanding of brain activity patterns that may be lost in averaged data. Here we discuss the typical approach as well as the more modern Hidden Markov Models.

4.11.1 Conventional burst analysis

Conventional burst analysis relies on thresholding techniques to identify bursts in neural activity. This involves setting a threshold on the Hilbert envelope of the signal (Little et al., 2019), and any activity exceeding this threshold is considered a burst. While thresholding methods are straightforward to implement, they can be sensitive to the choice of threshold and may not capture the complex dynamics of bursting behaviour. Moreover, thresholding is typically applied to signals filtered to single frequency band, this can be misleading as bursts may have frequency content spanning more than one band. Despite these limitations, thresholding methods have been widely used in MEG research to investigate bursting activity in various brain regions and cognitive processes. For example, bursts in the alpha frequency band have been linked to attention and working memory (Klimesch et al., 2007), while bursts in the gamma band have been associated with perceptual binding and object recognition (Tallon-Baudry et al., 1996).

4.11.2 Hidden Markov Models

Hidden Markov Models are versatile mathematical tools used across various fields, including finance, speech recognition, and biomedical imaging (Hassan and Nath, 2005; Rabiner, 1989; Rezek and Roberts, 2005). In neuroscience, HMMs have gained prominence for analysing electrophysiological data. Rezek and Roberts, 2005, established a general methodology for applying HMMs to biological signals. Woolrich et al., 2013, then applied HMMs to MEG data, identifying brief brain states lasting about 100ms. This led to innovations like temporally adaptive beamforming. HMMs have also been used to study functional connectivity in MEG data, revealing interactions between the default mode network and other transient brain states and also showing that canonical resting state networks modulate on millisecond timescales (Baker et al., 2014). Recent advancements involve more complex HMMs using multivariate autoregression and time-delay embedding, enabling the investigation of whole-brain dynamic networks based on spectral content (Quinn et al., 2018; Vidaurre et al., 2018, 2016).

4.11.3 Markov chains

To understand the practical application of HMMs to MEG analysis, we must first cover the concept of Markov chains. Named after Russian mathematician Andrey Markov, they are mathematical systems that describe transitions from one state to another according to certain probabilistic rules. A key feature of a Markovian chain is that the probability of transitioning to a particular state depends solely on the current state and not on the sequence of events that preceded it. This "memoryless" property, known as the Markov assumption, is fundamental to the model inference. For a sequence of states $q_1, q_2, \dots, q_i$, this property can be formally expressed as

$$P(q_i = a | q_1 \dots q_{i-1}) = P(q_i = a | q_{i-1}). \quad [4.49]$$

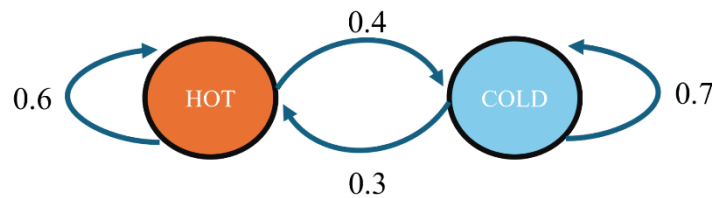


Figure 4.10: Two-state Markov chain. The arrows indicate the direction of the transition between states and the numbers describe the probabilities of those transitions occurring.

Graph representations can be very helpful in describing Markov chains. As illustrated in Figure 4.10, states are depicted as nodes and the transition

probabilities, as edges. Here, we are using the Ice Cream Climatology example from Eisner, 2002. The goal of this task is to estimate the weather on any given day provided a set of observations. Using the key elements of a Markov chain, we can very easily describe this system. First, by choosing a set $Q = q_1, q_2 \dots q_N$ made up of N states. In our case, these are hot or cold days. Secondly, the likelihood of each transition can be captured by a transition matrix T in which each element T_{ij} corresponds to the probability of going from state i to state j . In our example, this would result in

$$T = \begin{bmatrix} 0.6 & 0.4 \\ 0.3 & 0.7 \end{bmatrix} \quad [4.50]$$

where values along the diagonal are the probabilities for remaining in the same state. We can use these values to calculate the probability of any given sequence of states. This calculation does require one more component, the stationary distribution vector π_0 . For an infinite Markov chain, this vector describes how much time is spent of each state, which is equivalent to the likelihood that a given sequence will start with a certain state. These values can be derived by finding the normalised left eigenvector of T , formally defined as

$$\pi_0 T = \pi_0, \quad [4.51]$$

which for our example is

$$\pi_0 = [0.43 \ 0.57]. \quad [4.52]$$

Using these tools, we can estimate the probability of any sequence. For example, the probability of having two hot days and a cold one would be

$$P([hot, hot, cold]) = 0.43 \cdot 0.6 \cdot 0.4 = 0.1032. \quad [4.53]$$

4.11.4 Hidden states

The Markov chain we have discussed thus far offers a very simplistic model. In practice, the data we are interested in is typically affected by noise and may not be a direct representation of the states that we want to study. To address this, HMMs extend the Markov chain framework by incorporating hidden states. Figure 4.11 shows how hidden states dictate the observed sequence of data. In Eisner's example, weather data for a specific town has gone missing, and all we have for reference is Eisner's diary, which details how many ice creams he ate each day while living there. Since the weather "states" are not directly observable, our goal is to use the observations at hand (in this case the number of ice creams consumed) to guess the underlying weather sequence. This new hidden layer incorporates a set of emission probabilities, which describe the

probability that a given state will produce each of the possible observations. As shown in Figure 4.11, hot days are more likely to be those on which Eisner had more ice creams.

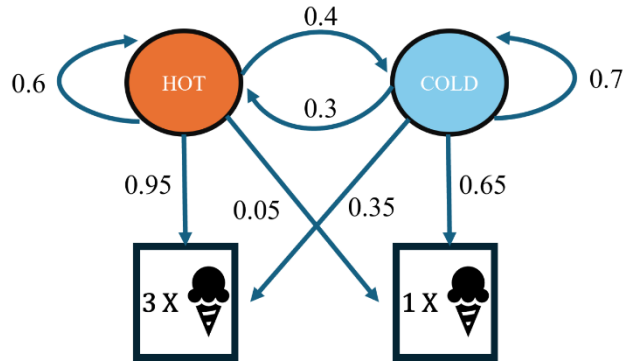


Figure 4.11: Hidden Markov model diagram. The hidden states produce the observations given the probabilities indicates by the arrows.

Similar to the transition matrix, we can describe the probabilities of each observation being a result of being in any given state with an emission matrix E such that

$$E = \begin{bmatrix} 0.95 & 0.05 \\ 0.35 & 0.65 \end{bmatrix}. \quad [4.54]$$

Here, each element E_{ij} corresponds to the probability of making an observation Y_i , given that the current state is X_j . In our example, the possible observations are Eisner having either 1 or 3 ice creams. With this information, we can attempt to guess the weather from the information in Eisner's diary, exemplified as the sequence shown on Figure 4.12.

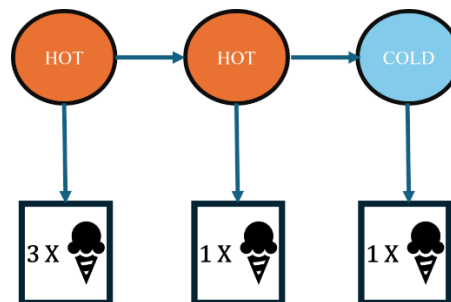


Figure 4.12: Example sequence of observations and active states.

First, we define a sequence of observations $Y = Y_1, Y_2, Y_3$ resulting from a sequence of states $X = X_1, X_2, X_3$. Using Bayes' theorem, we can obtain an expression for the joint probability $P(X, Y)$ of any sequence of T observations

Y , induced by a specific sequence of N active states X . Starting from the definition $P(X, Y) = P(Y|X)P(X)$ and making the appropriate substitutions gives

$$P(X, Y) = P(X_0) \prod_{i=1}^{N-1} P(X_i|X_{i-1}) \prod_{i=0}^T P(Y_i|X_i), \quad [4.55]$$

where $P(X_0)$ is the initial state probability, which is contained in π_0 (Jurafsky and Martin, 2009). From this, we may calculate the probability of the sequence illustrated in Figure 4.12, which is

$$\begin{aligned} &P([hot, hot, cold] [3, 1, 1]) \\ &= 0.43 \cdot (0.6 \cdot 0.4) \cdot (0.95 \cdot 0.05 \cdot 0.65) \\ &\cong 0.0032 \end{aligned} \quad [4.56]$$

While this is a useful example, in practice, we would not necessarily know the sequence of hidden states that resulted in our set of observations. This problem could be solved by calculating all possible state sequences for this particular sequence of observations and finding the state sequence that results in the highest joint probability $P(X, Y)$. Formally, this can be expressed as

$$\operatorname{argmax}_{X=x_1, x_2, \dots, x_N} P(X = x_1, x_2, \dots, x_N | Y = y_1, y_2, \dots, y_N). \quad [4.57]$$

This algorithm, however, has an exponential increase in runtime. For a HMM composed N hidden states with T observations, the number of possible hidden state sequences is N^T . If we were dealing with time series data with many datapoints, this solution quickly becomes very inefficient. There are a number of ways to overcome this issue, the most common one being the forward algorithm, which calculates the probability of a sequence of observations by summing the probabilities of all possible state paths. This results in a much faster computation time ($O(N^2T)$) for each possible state sequence (Jurafsky and Martin, 2009).

4.11.5 Model inference

It is important to note that this last scenario hinges on a significant assumption: knowing of the set of hidden states, as well as their transition and emission probabilities. These unknowns define the HMM and fortunately, they can be estimated from the data alone with the help of some prior assumptions. For an HMM of K hidden states and length T , the set of model parameters is formally defined as $\theta = \{\theta_1, \dots, \theta_T\}$, and the set of hidden state variables, as $S =$

$\{S_0, \dots, S_T\}$. The model parameters θ dictate both the observation probability at each time point and the transition likelihood between successive steps. These include π , the transition probability matrix of size $K \times K$, made up of elements $\pi_{t_{t-1}}$ which contain the state transition probability $P(S_t|S_{t-1})$. Again, π_0 determines the initial state probability $P(S_0)$. Lastly, θ_{obs} correspond to the observation probabilities $P(Y_t|S_t)$. The full posterior probability of the model including all these elements can then be defined as

$$P(Y, S, \theta, \pi) = P(S_0|\pi_0) \prod_{t=1}^T P(S_t|S_{t-1}, \pi) P(Y_t|S_t, \theta) P(\theta) P(\pi), \quad [4.58]$$

where $P(\theta)$ and $P(\pi)$ are non-informative priors, and $P(Y_t|Y_{t-1}, \theta)$ is the observation model (Woolrich et al., 2013). This model relates the observations to the hidden states, describing how the data is distributed over each of the states.

Having defined all the elements that comprise the HMM, we can now turn to how to best apply it to our MEG data. The problem at hand is two-fold. First, we need to estimate the hidden variables $H \equiv \{S, \theta, \pi\}$ that most accurately explain our observed data. Second, we must solve what is known as the decoding problem: determining the specific sequence of hidden states that generated our observations.

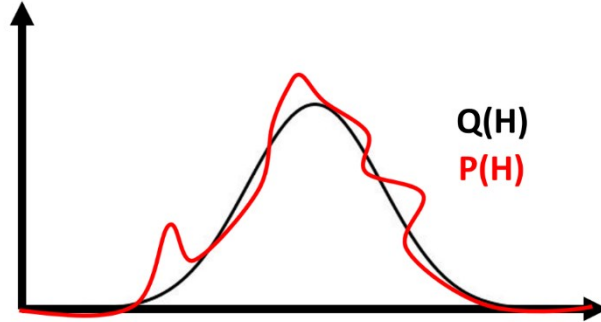


Figure 4.13: Model parameter distributions diagram. The distance between the estimate $Q(H)$ and the real distribution $P(H)$ is calculated as the Kullback-Leibler divergence and minimised to optimise $Q(H)$.

The first problem can be addressed by using variational Bayes inference. Consider the actual distribution of hidden variables $P(H)$ and our approximation $Q(H)$. As shown in Rezek and Roberts, 2005, one can use Kullback-Leibler divergence to calculate the distance between both distributions. Often called the variational free energy, it takes the form

$$\mathcal{F} = \int Q(H) \log \frac{Q(H)}{P(H|V)} + \log P(V), \quad [4.59]$$

where V is the set of observations. As shown on Figure 4.13, the real distribution $P(H)$ may be impossible to calculate, but by minimising $\mathcal{F}$, we can optimise $Q(H)$ so that it best approximates the hidden variables. Arriving to such a solution requires making one key assumption, which is that each of the hidden variables is independent of each other. This means that $Q(H)$ can be expressed as

$$Q(H) = \prod_i Q_i(H_i) \quad [4.60]$$

for each separate distribution Q_i of each variable H_i . From this, the update formulae can be derived and applied to estimate Q_i . This algorithm can be sequentially implemented for all $Q_i(H_i)$, ultimately optimising Q until a convergence threshold is reached. The general form of the update formula is

$$\log(Q_i(H_i)) = \int Q_{j \setminus i}(H_{j \setminus i}) \log P(Y, H) dH_{j \setminus i}, \quad [4.61]$$

where $j \setminus i$ indicates the integral is calculated for all j except $j = i$ (Haft et al., 1999; Rezek and Roberts, 2005). This is equivalent to fixing all variables except H_i .

Having established how to estimate the model parameters, we can now discuss the decoding task: determining the most likely sequence of hidden states that generated our MEG observations. One might initially consider a brute-force approach: use the forward algorithm to compute observation likelihoods for each possible hidden state sequence, then pick the sequence with the highest likelihood. However, this approach quickly becomes impractical. As we saw earlier, the number of possible state sequences grows exponentially with time, making exhaustive computation infeasible. The most common approach is Viterbi decoding. This algorithm provides an efficient way to find the optimal sequence of hidden states by maximizing the joint probability of the states and observations. Unlike forward-backward algorithms that compute probabilities for each state independently, Viterbi decoding finds the single most probable sequence of states that explains our entire observation sequence. In our case, the timecourse u_t for each state is calculated as

$$u_t = \operatorname{argmax}_k P(S_t = k|Y), \quad [4.62]$$

where u_t is the most likely a posterior state at each time point t . The probability of each state at each timepoint is calculated using the Viterbi algorithm (Woolrich et al., 2013).

4.11.6 The observation model

Having discussed the learning and decoding problems, it is also important to consider the observation model $P(Y_t|S_{t-1}, \theta)$. While simple HMMs (such as the one we discussed initially) use an emission matrix for observations, more sophisticated approaches are needed for complex data like brain signals. Consider the Gaussian observation model: here, each state generates observations from a normal distribution, with state-specific mean and variance parameters. This approach has been applied successfully in the literature by defining the priors as conjugate distributions (Rezek and Roberts, 2005; Woolrich et al., 2013). However, this method does not come without limitations. The Markov property assumes each observation only depends on the previous moment in time. For brain signals, this assumption is often unrealistic, as neural activity typically shows longer-term dependencies.

More sophisticated approaches have been developed over the years. such as multivariate autoregressive models (Penny and Roberts, 2002; Vidaurre et al., 2016) or the time-delay-embedded HMM (TDE-HMM). This last method, introduced in Vidaurre et al., 2018, offers an elegant solution. Rather than examining isolated time points, the TDE-HMM analyses temporal windows of activity, computing signal autocovariance across multiple time lags. This method effectively characterizes the spectral patterns within each temporal window, making it especially suitable for MEG data analysis. Given its advantages in capturing neural dynamics, we employed the TDE-HMM approach for the experimental investigations presented in Chapter 5.

Chapter 5 Magnetic shielding

As discussed, optimal OPM performance requires a low magnetic field environment. This chapter covers the physics and design criteria of the magnetic shielding systems that enable OPM-MEG. We first discuss the use of multilayered MSRs. Key concepts describing the performance of passive shielding are introduced by applying laws from classical electromagnetism. Secondly, active shielding systems are described in detail, as they constitute a big part of the experimental work presented in this thesis.

5.1 Introduction

As previously stated, external magnetic noise sources, such as power lines, electronic devices, and geomagnetic disturbances, can significantly degrade the SNR of MEG recordings. Magnetic shielding and signal processing techniques aim to reduce the influence of these external sources on the MEG data. As detailed in previous sections, traditional cryogenic MEG systems primarily rely on the use of gradiometers and passive shielding. The latter comes in the form of MSRs, made up of multiple layers of high-permeability magnetic materials, such as mu-metal (Budker and Kimball, 2013).

When operating in the SERF regime, even minor background field changes can significantly alter spin-exchange collision relaxation rates in OPMs. Additionally, cross-axis projection errors (CAPEs) demand extremely stable magnetic conditions (± 1.5 nT). Sharp field variations can compromise the sensor's linear response and gain, potentially introducing measurement errors (Borna et al., 2022). For example, when measuring along a single axis like B_x , magnetic field changes in orthogonal axes (B_y and B_z) can appear as a fictitious change in B_x .

OPM-MEG is sensitive to subject movement in a unique manner since the sensors move along with the subject (Holmes et al., 2023b). This means background magnetic field magnitude can significantly influence data quality. Although MSRs do a lot of the heavy lifting when it comes to removing background interference, there are still remnant fields in the rooms. Movement artifacts become more pronounced when a subject moves their head in regions with spatially varying magnetic fields. The use of active magnetic shielding to suppress these remnant fields has therefore been key in realising the potential of OPM-MEG. The recent addition of closed loop operation to QuSpin's QZFM sensors can also alleviate the same problem by keeping the sensors voltage response within its linear regime (Schofield et al., 2024).

5.2 Passive shielding

Typically constructed as metallic enclosures, passive shields are engineered to attenuate electromagnetic radiation. The use of electromagnetic shielding can be dated back to the development of the first telegraph and radio systems, where cables had to be sleeved with a wire mesh to stop leaking of signals as well as reduce interference. The proliferation of consumer electronics has made the use of shielding quite common, normally found in mobile phones or around any magnetically sensitive components, like hard drives. In medical imaging, MRI systems employ sophisticated magnetic shielding to contain powerful magnetic fields generated by superconducting magnets, preventing stray magnetic radiation from affecting surrounding equipment and personnel while also attenuating external interference (Ishiyama and Hirooka, 1991). The performance of such shields can be simply quantified as the ratio between the magnitude of the field outside (B_0) and inside (B_s) the shielded volume:

$$SF = \frac{|B_0|}{|B_s|}, \quad [5.1]$$

where SF is known as the shielding factor (Hoburg, 1995). A larger shielding factor indicates greater attenuation of the background magnetic field. This is normally quantified in decibels, as given by:

$$SF = 20 \log_{10} \frac{|B_0|}{|B_s|}. \quad [5.2]$$

5.2.1 Magnetically shielded rooms

In the context of MEG, passive shielding is achieved through the use of MSRs. They are carefully designed cuboid enclosures that provide sufficient space to accommodate both the sensing apparatus and the research subject. The walls are made up of alternating layers of ferrite materials and conductive materials, like copper. Ferrite materials are utilised due to their high relative permeability. Analogous to conductivity, this quantity defines how easily a material can be magnetised by an external magnetic field. Normally, the flux of a magnetic field in free space is defined as

$$B = \mu_0 H, \quad [5.3]$$

where μ_0 is the permeability of free space and $\mathbf{H}$ is the magnetic field strength in Amperes per meter. However, this expression is not accurate in the presence of a magnetised material, which alters the spatial distribution of $\mathbf{B}$. In that case, the magnetic field flux is given by:

$$\mathbf{B} = \mu_0 \mu_r \mathbf{H}, \quad [5.4]$$

where μ_r is the material's relative permeability. This is defined as

$$\mu_r = 1 + \chi = 1 + \frac{\mathbf{M}}{\mathbf{H}}, \quad [5.5]$$

where the magnetic susceptibility χ is defined as the ratio between the magnetisation $\mathbf{M}$ of the material and the $\mathbf{H}$ field. The susceptibility of a ferromagnetic material determines the shape of its $\mathbf{B}$ - $\mathbf{H}$ curve, also known as its hysteresis cycle. The plot on Figure 5.1 illustrates this phenomenon. As the external field $\mathbf{H}$ is increased, the magnetic moments within the crystal structure's magnetic domains progressively align. This alignment generates a cumulative net magnetization that continues to intensify until the material reaches magnetic saturation, a state where no further magnetization is possible. As shown in the plot below, this behaviour is non-linear and irreversible. Decreasing the field yields different values of $\mathbf{B}$, meaning that the material's magnetisation not only depends on the applied field, but also on its previous magnetisation.

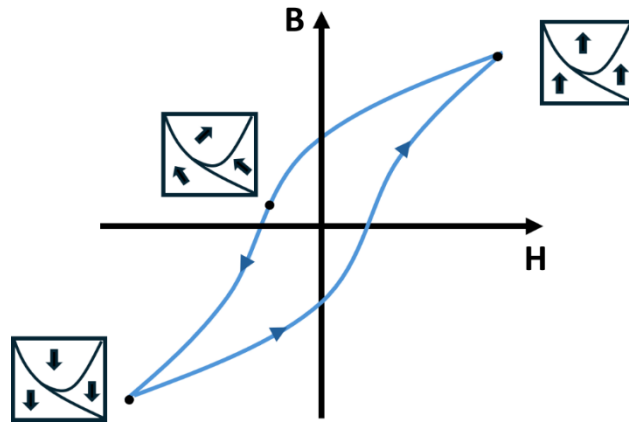


Figure 5.1: Hysteresis cycle diagram: as the magnetic domains align, the total magnetisation of the material peaks. Reversing the applied magnetic field will yield different magnetisation values, following the hysteresis loop.

5.2.2 Flux shunting

Passive shields aim to mitigate both time varying (AC) and static (DC) fields. Flux shunting is what makes high permeability materials ideal to mitigate static and low frequency (<10 Hz) fields. Rather than cancelling the external magnetic fields, this phenomenon redirects them. The presence of a high permeability material provides an alternative, low-resistance path for magnetic flux. This effect is depicted on Figure 5.2A for the cross-section of a cylindrical shield. By strategically layering materials with high magnetic permeability, passive shields can effectively "guide" magnetic field lines away from a protected region, significantly reducing the magnetic field intensity within the shielded space.

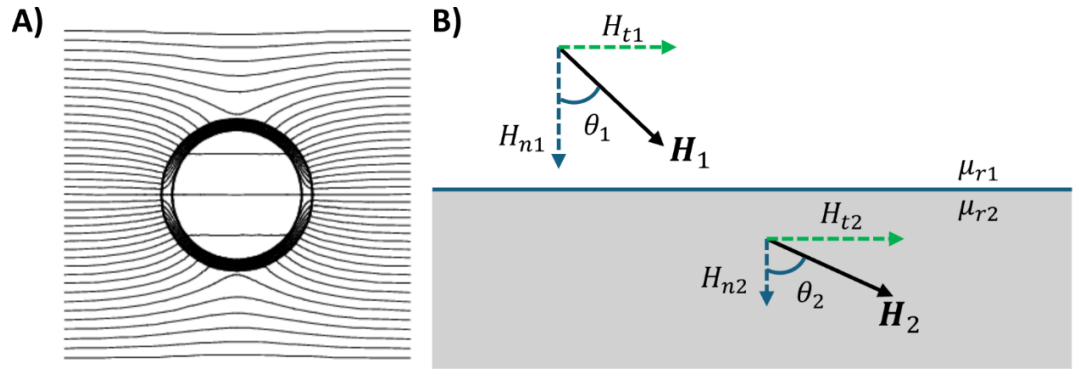


Figure 5.2: Flux shunting: **A)** Illustration depicting magnetic field lines around a cylinder of ferromagnetic material. Adapted from Celozzi et al., 2008. **B)** Diagram of flux shunting for a magnetic field $\vec{H}$ crossing a boundary between mediums of different magnetic permeabilities, where the dashed arrows represent the tangential $\vec{H}_t$ and normal components $\vec{H}_n$.

Flux shunting is a consequence of Maxwell's equations. First, Gauss' law states ensures that the magnetic field lines always form closed loops. This means that the component of $\vec{B}$ normal to the surface, B_{norm} , must be continuous at the boundary. Similarly, Ampere's law states that the tangential component of $\vec{H}$ must also be continuous at the boundary. This results in two boundary conditions:

$$\begin{aligned}\mu_{r1}H_{n1} &= \mu_{r2}H_{n2}, \\ H_{t1} &= H_{t2}\end{aligned}\tag{5.6}$$

where the suffix numbers 1 and 2 refer to components before and after crossing the boundary. A diagram of the vector fields is shown in Figure 5.2B, where the angle of incidence of the $\vec{H}$ field is defined as θ_1 . Using the boundary conditions

in 5.6, we can derive an expression for the outgoing angle θ_2 , which takes the form:

$$\theta_2 = \arctan\left(\frac{\mu_2}{\mu_1} \tan \theta_1\right) \quad [5.7]$$

where μ_1 and μ_2 are the relative permeabilities of both mediums. This transformation depends on the ratio of permeabilities, if μ_2/μ_1 is greater than 1, the magnetic field lines will be "compressed" or bent following the surface of the material. If μ_2/μ_1 is less than 1, the magnetic field lines will be "expanded" or bent away from the normal. It then follows that using ferrite materials of high relative permeability to enclose a volume of interest will guide the magnetic field lines around the space, effectively reducing the background field.

5.2.3 Eddy current shielding

An additional shielding mechanism is provided by eddy currents. This electromagnetic phenomenon provides an additional layer of protection against time varying fields. It is a direct consequence of Faraday's law:

$$\nabla \times \mathbf{E}(t) = -\frac{\partial \mathbf{B}(t)}{\partial t}, \quad [5.8]$$

which states that, as the external magnetic field $\mathbf{B}$ oscillates, it induces an electric field $\mathbf{E}$ in the material. Lenz law also tells us that in electrically conductive materials, the induced electric fields generate eddy currents proportional to the material's conductivity. These currents generate their own secondary magnetic fields that effectively counteract and attenuate the incident magnetic field (Figure 5.3A). This is why MSRs are assembled of both highly permeable materials as well as highly conductive materials, like copper or aluminium. The resulting effect on magnetic field lines is depicted in Figure 5.3B.

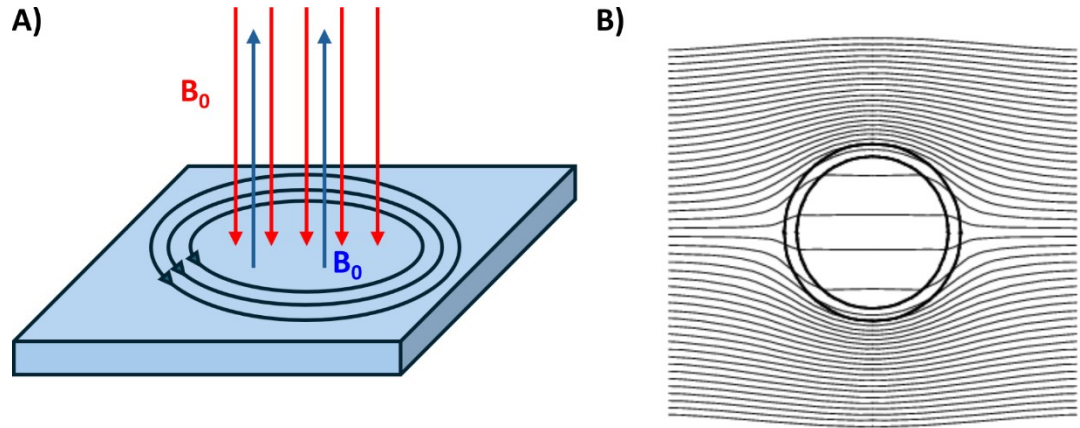


Figure 5.3: Eddy current shielding: A) Diagram illustrating the currents induced in a conducting material by an external magnetic field B_0 . The currents produce an opposing magnetic field B_i . B) Diagram showing the effect of eddy current shielding on magnetic field lines around a cylindrical shield. Adapted from Celozzi et al., 2008.

The effectiveness of eddy current shielding depends on several critical material properties. Conductivity plays a crucial role, with highly conductive materials like copper and aluminium demonstrating superior shielding performance. The thickness of the conductive material also significantly influences shielding effectiveness. Throughout the material thickness, the induced eddy currents decay exponentially. The extent to which most of the current will flow within shielding material is known as the skin depth:

$$\delta = \sqrt{\frac{2}{\sigma\omega\mu_r\mu_0}}. \quad [5.9]$$

where σ is the material's conductivity and $\omega = 2\pi f$ is the frequency of the incident magnetic field (Celozzi et al., 2008). For example, at 50 Hz copper has a skin depth of around 8.5 mm while aluminium's is around 10.5 mm. Although thicker shields can generate more extensive eddy currents, providing greater magnetic field attenuation, these values suggest that there's a point of diminishing returns. Beyond the skin depth, additional material yields only minor improvements in shielding performance. Meanwhile, this significantly increases both weight and cost of the shield. Regardless, larger continuous shields can also exhibit stronger shielding since the eddy current are able to spread over a larger volume to counter the incident fields. Lastly, it is worth noting that frequency characteristics are another essential consideration in eddy current shielding. As per equation 5.9, eddy currents are less effective at lower frequencies, while at higher frequencies, the induced currents become more pronounced and generate stronger opposing magnetic fields. This frequency-dependent behaviour means that eddy current shielding is particularly effective for high-frequency electromagnetic interference.

5.2.4 Spherical shield

Shield geometry plays a critical role in passive magnetic shielding, influencing the effectiveness of magnetic field attenuation and redirection. The shape, thickness, and configuration of magnetic shield materials determine how efficiently external DC magnetic fields can be redirected away from sensitive regions. A common example to illustrate the role of these properties is a spherical shield (Figure 5.4).

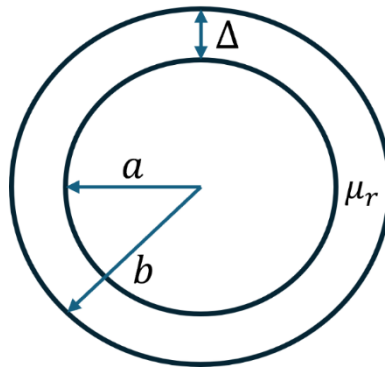


Figure 5.4: Spherical shield diagram. The dimensions are indicated by a , the inner radius, b , the outer radius and thickness Δ .

An analytical solution for the shielding factor of a spherical shield was found by Hoburg, 1995. This solution assumes the relative permeability of the material to be constant, which results in a constant shielding factor of

$$SF = \frac{(\mu_r + 2)(2\mu_r + 2) - 2\frac{a^3}{b^3}(\mu_r - 1)^2}{9\mu_r}, \quad [5.10]$$

where a and b are the inner and outer radii, respectively. The expression can be further simplified if one assumes that the thickness of the shield is much smaller than its radius. This means that $\mu_r \frac{\Delta}{a} \gg 1$, where we define Δ as $b - a$. In this case, equation 5.10 becomes:

$$SF \approx \frac{2}{3}\mu_r \frac{\Delta}{a} + 1, \quad [5.11]$$

Using this expression, we can predict the shielding factor for spherical shields of varying permeabilities and dimensions. As shown in Figure 5.5, higher permeabilities and thicker spherical shells dramatically improve shielding performance.

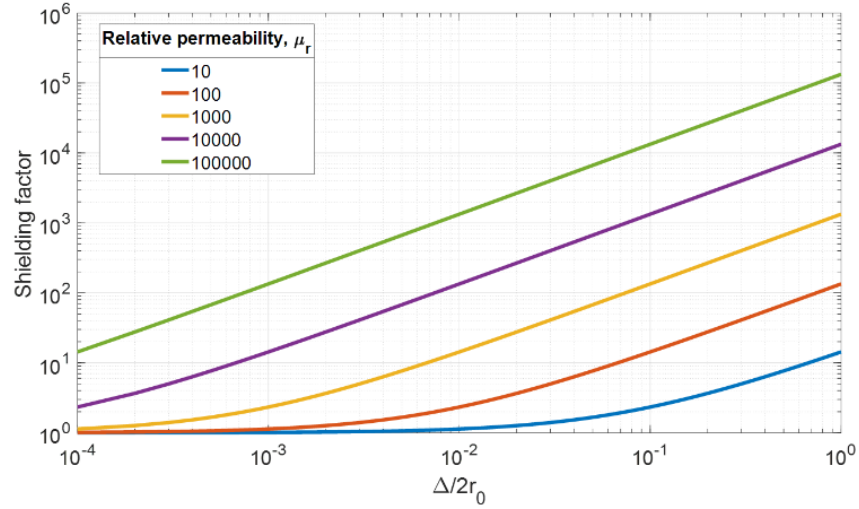


Figure 5.5: Simulation results estimating the shielding factor for sperical shields of increasing thickness to diameter ratios. Each line represents results for different magnetic permeabilities. Adapted from Edwards, 2024..

Cylindrical and cuboid shield geometries are among the most common designs, with each offering unique advantages depending on the desired application. The efficiency of such shields is typically improved by using multiple layers, essentially adding concentric shells alternating between ferrite and highly conductive materials. For a two-layer spherical shield, equation 5.10 becomes

$$SF = 1 + S_1 + S_2 + S_1 S_2 \left(1 - \left(\frac{d_2}{d_1} \right)^3 \right), \quad [5.12]$$

where S_1 and S_2 are the shielding factors for each shell, and d_1 and d_2 are their diameters (Mager, 1970). The shielding factor of each shell can be estimated using

$$S = \frac{4\mu_r}{3d} \Delta d \quad [5.13]$$

Lastly, it worth noting that the presence of seams or joints between the metal plates can affect the passing of eddy currents or the redirected magnetic

fields. Although the use of welds or joints is unavoidable, particular attention must be paid to joint design and implementation to ensure optimal shielding integrity.

5.2.5 Demagnetisation

As previously discussed, ferrite materials can be magnetized in the presence of an external magnetic field. This means that for optimal shielding performance, the magnetisation of the shielding material must be driven to zero, since any remnant magnetization worsen the shielding performance of the material. Fortunately, several demagnetization techniques can be employed to eliminate or minimize the material's magnetic memory.

A common approach is alternating field demagnetization, or degaussing. This technique was first developed during World War II to avoid magnetic naval mines by essentially reducing unwanted residual magnetization in materials. As shown in Figure 5.6A, the process involves exposing the material to an alternating magnetic field of decreasing amplitude, causing magnetic domains to gradually randomize until reaching a state of zero net magnetization. This technique is particularly useful for complex-shaped shields or materials where uniform thermal treatment might be challenging. Since the permeability of the material is determined by the gradient of the ***B-H*** curve, one should aim to maximise μ_r by operating at the point where ***B = H = 0***, as this corresponds to the steepest gradient on the curve, thereby yielding the highest possible permeability value. The oscillating fields employed to drive this transition can be produced by a set of coils which surround the ferrite layers. A typical setup, shown in Figure 5.6B, uses L-shaped coils mounted on the top and bottom faces of a cubic-shaped shield (Altarev et al., 2015).

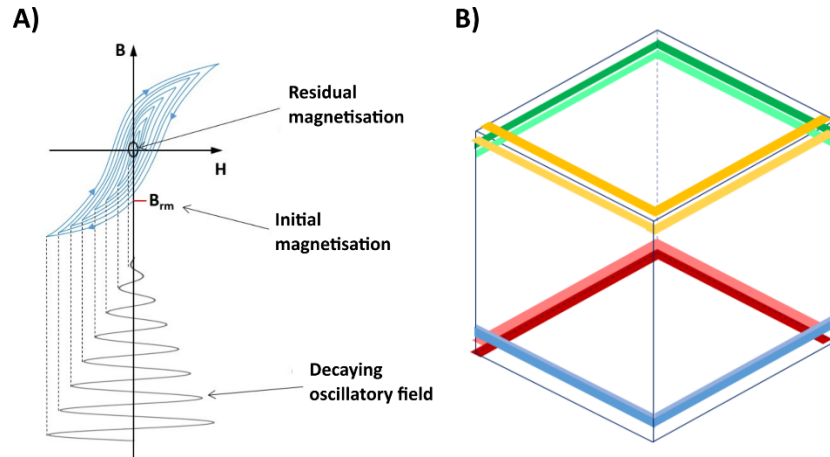


Figure 5.6: **A)** Demagnetisation diagram. A decaying oscillatory field can be employed to drive the magnetisation of a ferromagnetic material towards zero. **B)** Diagram of L-shaped coils used to demagnetise a cuboidal shield. Adapted from Edwards, 2024.

Additionally, thermal processes such as annealing are typically used to improve shielding efficiency during the manufacturing process of the ferrite layers. The ferrite material is heated above its Curie temperature, a critical point at which thermal energy disrupts the magnetic domain alignments (Spasojević et al., 2024). By carefully controlling the heating and cooling process, the magnetic domains can be randomized, effectively resetting the material's magnetic state. Additionally, annealing is normally performed in a hydrogen rich environment which helps remove impurities and stresses, which results in a higher permeability (Masuzawa et al., 2013).

5.3 Active shielding

We have discussed how passive shielding can solve a lot of our problems when dealing with AC and DC fields, but it is still not perfect. Even following degaussing, small magnetic fields (2-10 nT) can remain inside the shield due to external influence or small remnant magnetisation. Although such background fields would be sufficient for stationary OPM-MEG operation, low-frequency variations in these fields can pose an additional challenge. Sources like passing vehicles or nearby elevators can cause field fluctuations of ± 1 nanotesla over 10 minutes or even ± 5 nanoteslas in just a few seconds. Participant movement can also manifest as a low frequency field since the sensors may move in a non-zero background field. The magnitude and character of these artefacts depend heavily on the source and its proximity to the shield.

5.3.1 Coil systems

To tackle these persistent magnetic field variations, electromagnetic coils can be utilised to generate a precisely counterbalanced magnetic field. Analogous to a noise-cancelling headphone system: these coils create a field that is exactly equal and opposite to the unwanted magnetism in the measurement space. Typically, this involves an array of coils - three to generate uniform magnetic field components and five more to produce linear spatial magnetic field gradients (Holmes et al., 2018a; Iivanainen et al., 2019a; Yoda, 1990). These magnetic field components can be described using Maxwell's equations. First, a magnetic field in free space obeys the following:

$$\begin{aligned}\nabla \cdot \mathbf{B} &= 0, \\ \nabla \times \mathbf{H} &= \mathbf{J},\end{aligned}\tag{5.14}$$

where $\mathbf{J}$ is the current density. If we assume that the volume of interest is free of moving charges, then the latter equation can be written as

$$\nabla \times \mathbf{B} = 0.\tag{5.15}$$

Evaluating this expression in cartesian coordinates involves expanding out the following

$$\begin{vmatrix} \mathbf{i} & \mathbf{j} & \mathbf{k} \\ \frac{\partial}{\partial x} & \frac{\partial}{\partial y} & \frac{\partial}{\partial z} \\ B_x & B_y & B_z \end{vmatrix} = 0.\tag{5.16}$$

The terms resulting from the expansion of 5.15 describe the spatially varying components of $\mathbf{B}$ as:

$$\begin{aligned}\frac{\partial B_x}{\partial z} &= \frac{\partial B_z}{\partial x} \\ \frac{\partial B_y}{\partial z} &= \frac{\partial B_z}{\partial y} \\ \frac{\partial B_x}{\partial y} &= \frac{\partial B_y}{\partial x} \\ \frac{\partial B_x}{\partial x} + \frac{\partial B_y}{\partial y} + \frac{\partial B_z}{\partial z} &= 0,\end{aligned}\tag{5.17}$$

Here, we find that the transverse spatial variation of each field component in one direction is identical to the variation of the other component in the complementary direction. These symmetries have important practical implications for magnetic shielding design, as they constrain how the field can vary in space. This is particularly crucial in applications such as MRI or quantum sensing experiments, where magnetic field control is critical. For example, image formation in MRI relies on spatial encoding of the Larmor frequencies through the use of magnetic field gradients. Design and construction of coils to produce such gradients has therefore been key in enabling MRI (Bowtell and Robyr, 1998; Turner, 1993). It follows that the theoretical principles underlying active shielding design overlap those used in gradient coil development.

Practical implementation of coil systems can vary widely depending on the needs of each particular application. The simplest example are Helmholtz coil pairs, consisting of two parallel circular coils with equal current flowing in the same direction, provide uniform magnetic fields along their axis (Abbott, 2015). Longitudinal gradients can be generated along the axis of the coil pair by reversing the current in one of the coils. The resulting field cancels out at the centre of the coils, and it increases or decreases linearly towards each coil. An example of this is shown in Figure 5.7B. Developed by Iivanainen et al., 2019, this setup consisted is a set of 8 square coil arranged in a cage around an array of OPMs. Using the output from the sensors, background fields of up to 70 nT were reduced to <1 nT. Placing coil pairs along orthogonal directions can be used to generate gradients $\frac{\partial B_x}{\partial x}$, $\frac{\partial B_y}{\partial y}$ and $\frac{\partial B_z}{\partial z}$. Transverse gradient coils ($\frac{\partial B_x}{\partial y}$, $\frac{\partial B_x}{\partial z}$ and $\frac{\partial B_y}{\partial z}$) can also be constructed using a planar projection of Golay's cylindrical coils (Golay, 1958; Roméo and Hoult, 1984; Tsai et al., 2008).

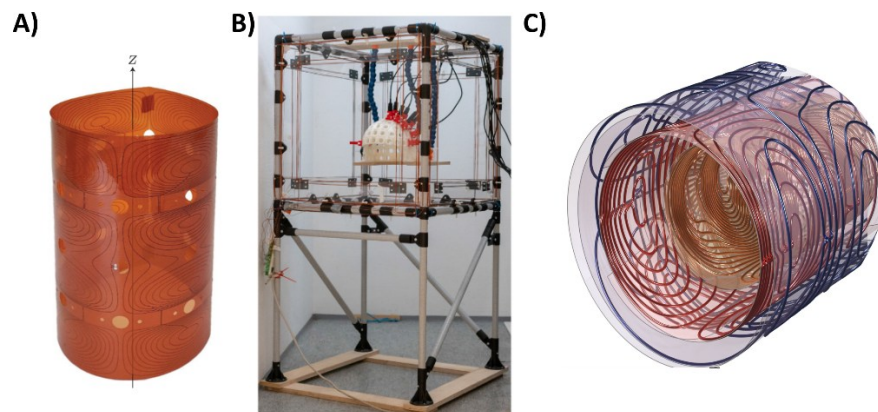


Figure 5.7: Examples of coils systems: *A) Flexible PCB coil for a small cylindrical shield developed by Hobson et al., 2023. B) Field compensation coils for OPM-MEG developed by Iivanainen et al., 2019a. C) Computer rendering of head gradient coils for brain imaging in a 7 Tesla magnet. Credit: Matthias Davids, University of Heidelberg and MGH Harvard, and David Feinberg, UC Berkeley (www.universityofcalifornia.edu).*

Distributed coil systems, traditionally used in MRI for generating homogeneous magnetic field gradients and signal detection, can be designed using stream functions under specific constraints (Turner, 1993). Wire paths are normally optimised to minimise energy usage and inductance (Carlson et al., 1992; Turner, 1993). This approach enables the creation of intricate wire patterns on cylindrical surfaces that conform to MRI magnet bore geometries. An example application is shown in Figure 5.7C, where a head-specific gradient coil system was developed to generate controlled field gradients for functional brain studies (Feinberg et al., 2023). Beyond their conventional MRI applications, these distributed coil designs have been adapted for active magnetic shielding, particularly in quantum sensing experiments where precise background field cancellation is crucial. Figure 5.7A illustrates this, showing work by Hobson et al., 2023, who implemented flexible PCB-based cylindrical coils—a design particularly suited for small shields used to study OPM performance.

5.3.2 Bi-planar coils for OPM-MEG

Planar gradient coils have been previously used in MRI due to their relatively easy assembly and low inductance (Martens et al., 1991; Turner, 1993). As shown by Yoda, 1990, planar coil designs can be employed to shield the superconducting magnets from the stray fields generated by gradients. For use in MEG, the planar design is particularly useful for MEG due to the cuboidal shape of MSRs. Holmes et al., 2018, demonstrated this by developing a set of bi-planar coils to null background fields in a volume of interest to perform OPM-MEG measurements. Here, coil design methods as well as their operation are briefly described.

5.3.2.1 Coil design

In a similar approach to Carlson et al., 1992, the wire paths for the bi-planar coils were derived analytically by describing the required current density as a stream function constrained to the $|x|, |y| < L$ region on the planes $z = \pm a$ and forced to be zero at the edge of these planes. These correspond to the two planes to both sides of the participant (Figure 5.8). The stream function is defined as a two-dimensional Fourier series:

$$S(x, y) = \sum_{n=1}^N \left[\alpha_n \cos\left(\frac{\pi}{2}(2n-1)\frac{x}{L}\right) + \beta_n \sin\left(\frac{\pi nx}{L}\right) \right] \times \sum_{m=1}^M \left[\gamma_m \cos\left(\frac{\pi}{2}(2m-1)\frac{y}{L}\right) + \delta_m \sin\left(\frac{\pi my}{L}\right) \right], \quad [5.18]$$

where the α_n , β_n , γ_m , δ_m correspond to weights for each frequency contribution. Fortunately, symmetry conditions for each magnetic field component can help simplify this expression for each coil pair, thanks to our knowledge of simpler coil geometries such as Helmholtz coils. For example, the B_x coil should be anti-symmetric about $\hat{x}$ and $\hat{z}$, but symmetric about $\hat{y}$. This reduces the number of harmonic components required to describe the current density, so that expression 5.18 becomes

$$S(x, y) = \sum_{n=1}^N \sum_{m=1}^M \left[\lambda_{nm} \sin\left(\frac{\pi nx}{L}\right) \cos\left(\frac{\pi}{2}(2m-1)\frac{y}{L}\right) \right], \quad [5.19]$$

where λ_{nm} are the reduced coefficients for each harmonic contribution. The magnetic field is related to the stream function through the expression

$$\tilde{\mathbf{B}}(k_x, k_y, z) = \mu_0 \left\{ [ik_x \hat{x} + ik_y \hat{y}] \frac{\sinh(k_r, z)}{\cosh(k_r, z)} - k_r \hat{z} \frac{\sinh(k_r, z)}{\cosh(k_r, z)} \right\} \tilde{S}(k_x, k_y) e^{-k_r a}, \quad [5.20]$$

where $\tilde{\mathbf{B}}$ and $\tilde{S}$ are the magnetic field and the stream function in k -space, respectively, k_r is $(k_x^2 + k_y^2)^{1/2}$, and $z_{>,<}$ is the greater or lesser than z or a . The upper and lower $\sinh$ and $\cosh$ functions correspond to the field components for which the stream function has the same or opposite sign on each plane. The magnetic field in real space can then be found by taking the inverse Fourier transform of this last equation.

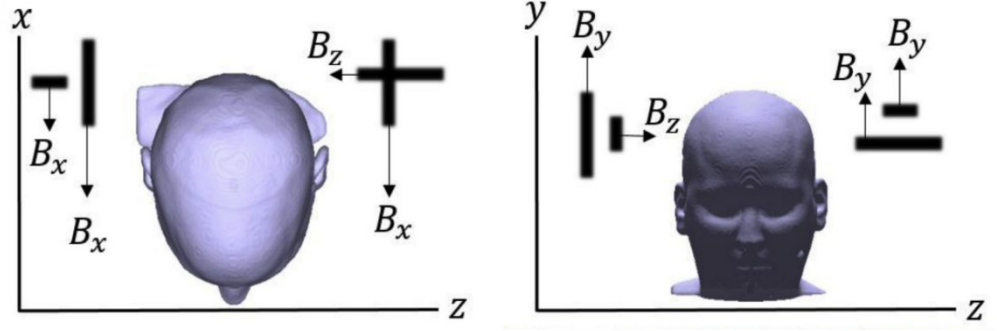


Figure 5.8: Coordinate system for the bi-planar coils.

Starting with these axioms, one can try find the desired wire paths for the B_x coil by taking the contour of 5.19 on the planes $z = \pm a$. This, however, requires finding the weights λ_{nm} . This is typically solved as a minimisation problem. In this case, Holmes et al., 2018 obtained the weights that minimised the difference between the desired field $B_x(\mathbf{r})$ and the calculated field $b_x(\mathbf{r})$ in the x direction. For a set of points $\mathbf{r}_i$ in the target volume, $b_x(\mathbf{r}_i)$ can be calculated for the j^{th} component of the stream function as

$$b_{xj}(\mathbf{r}_i) = 2DFT(i\mu_0 k_x \tilde{S}_j e^{-k_r a} \cosh(k_r z_i))|_{x_i y_i}, \quad [5.21]$$

where $j = (n - 1)N + m$. If one considers components $B_x(\mathbf{r})$ and $b_x(\mathbf{r})$, it is then possible to setup the minimisation problem by defining the functional F as

$$F = \sum_{i=1}^I |B_x(\mathbf{r}_i) - b_x(\mathbf{r}_i)|^2 + \omega P, \quad [5.22]$$

where P is a power dissipation term of amplitude ω (Carlson et al., 1992). Finally, the weights λ_j for the stream function can then be found by solving for $dF/d\lambda_j = 0$. This results in a set of linear simultaneous equations, which can be represented in matrix form, and used to solve for λ_j .

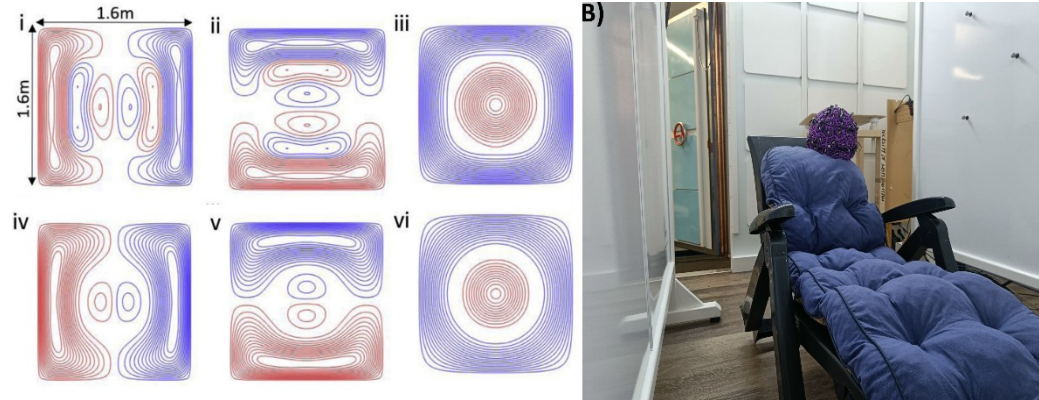


Figure 5.9: Bi-planar coil design: A) Wirepaths for i) B_x , ii) B_y , iii) B_z , iv) G_{xz} , v) G_{yz} , vi) G_{zz} coils. B) Bi-planar coil system in the MSR in the OPM-MEG lab at the University of Nottingham. The coils are shown at both sides of where the participants are typically seated.

Once the coefficients for the stream function are found, the same procedure can be utilised to find the wire paths for the remaining field components. The method described here was employed by Holmes et al., 2018, to construct six coils for the static components B_x, B_y, B_z and well as gradient components G_{xz}, G_{yz}, G_{zz} . The resulting wire paths are shown in Figure 5.9A, with a photo of the real setup for OPM-MEG shown on the right-hand panel. The coils were designed using a target volume of 40 cm^3 , with a varying number of harmonic components and target points to adjust the complexity of the wire paths. The power dissipation amplitude was optimized so that generated field had a $<5\%$ spatial deviation over the volume of interest. The setup is shown in Figure 5.9B, it allowed for easy access to the participant's chair, making it easy for researchers to set up paradigms prior to scanning.

The bi-planar coils were demonstrated to reduce the average magnitude of magnetic field over the target volume from 28 nT to 0.74 nT, drastically improving the quality of the MEG data. Lastly, it bears mentioning that the derivation for the coil wire paths can vary widely depending on the desired shield geometry, as well as the shape and size of the target volume and the desired field (Bowtell and Robyr, 1998; Carlson et al., 1992; Hobson et al., 2023). Additionally, one could also optimise the stream function to fit different requirements. This is often the case for MRI gradient coils, where researchers aim to minimise inductance, or the torque experienced by the coils.

5.3.2.2 Automated field cancellation

As previously outlined, background magnetic fields may exhibit slow drifts, which can pose a problem when acquiring MEG data. External sources and head movements can introduce field variations of up to 5 nT during a scan. Fortunately, a solution to this problem was implemented for OPM-MEG

utilising the coils described above. As shown by Holmes et al., 2019a, background field cancellation can be achieved iteratively through a proportional integral derivative (PID) controller.

PID controllers are feedback control systems commonly used in industrial applications to control for variables such as temperature, pressure, flow rate, etc. They can be implemented in software, or directly in hardware as analogue systems. A PID loop is based on an error value $e(t)$, calculated as the difference between a desired setpoint s and a measured process variable $b(t)$. The output of a PID loop is calculated as the sum of three terms:

- Proportional: Produces an output proportional to the current error. Larger errors cause larger control actions. However, using only P control typically results in steady-state error.
- Integral: Accumulates past errors over time. This component eliminates steady-state error by continuing to increase/decrease the control output until the error becomes zero.
- Derivative: Predicts future error behaviour based on the current rate of change. This helps reduce overshoot and improves stability, though it can amplify noise.

These terms are combined in the classic PID formula:

$$I(t) = K_p e(t) + K_i \int_0^t e(\tau) \tau d + K_d \frac{de(t)}{dt}, \quad [5.23]$$

where each term is weighted by a tuning parameter K_p , K_i , K_d and added to obtain an output control signal $I(t)$ (Åström and Hägglund, 1995). The tuning parameters are typically determined through various tuning methods. This may be done through trial and error, or through model-based tuning, if a mathematical model of the system is available. The output signal can then be fed back into the system of interest to drive the error signal down. For example, a thermostat can be considered to be a PID controller, where the process variable is the current room temperature and the setpoint is the desired temperature.

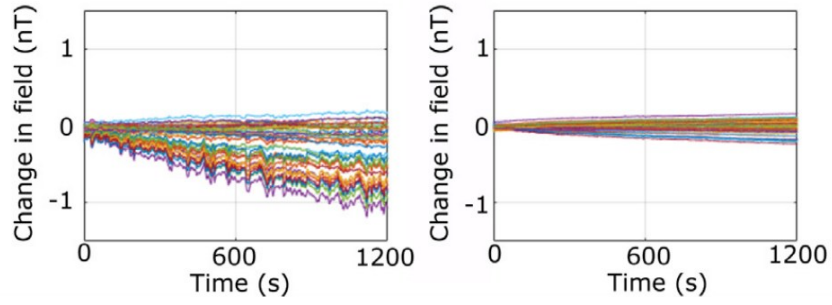


Figure 5.10: Dynamic nulling: Data collected using 40 optically pumped magnetometers in a rigid helmet within an unoccupied magnetically shielded room, comparing results without dynamic stabilization (left side) and with dynamic stabilization enabled (displayed on the right side). Figure adapted from (Rea et al., 2021a).

Due to their ability to control variables in a data-driven manner, PID controllers are particularly useful for field control in OPM-MEG. This was implemented using an array of 4 dual-axis QuSpin OPMs. The sensors are arranged to obtain measurements of the B_y , B_z as well as the gradients G_{xz} , G_{yz} , G_{zz} . The output data is then fed into a PID loop which controls the currents going through the bi-planar coils. The loop runs until the background field is reduced significantly, down to magnitudes of around 50 pT. Once the currents are fixed, the reference sensors can then be used to continuously track changes in the background field. As shown in Figure 5.10, these drifts can also be compensated using a PID controller, effectively ensuring that the OPMs are not saturated by large background field variations. Additionally, the reference array data can be recorded and utilised during post-processing as a synthetic gradiometer (Boto et al., 2017).

5.3.2.3 Improved field control via precise mapping

As demonstrated in previous work (Mellor et al., 2021; Rea et al., 2021a), an additional field mapping procedure beyond the use of just two measurement points with a reference array can be employed to further diminish the background field. This technique accurately maps the background field in the target volume, potentially eliminating the need for a reference array. For this, a spherical harmonic model was employed. Spherical harmonics provide a solution to the Laplace equation:

$$\nabla^2 \phi(x, y, z) = 0, \quad [5.24]$$

which can be used to describe a magnetic scalar potential $\phi(x, y, z)$ in a current free region. This condition is equivalent to Gauss's law for magnetism, which states that a magnetic field's divergence is equal to zero

$$\nabla \cdot \mathbf{B} = 0, \quad [5.25]$$

where

$$\mathbf{B}(x, y, z) = -\nabla\phi(x, y, z). \quad [5.26]$$

The solution for $\mathbf{B}(\mathbf{r})$ is typically expressed in spherical coordinates and takes the form

$$\mathbf{B}(\mathbf{r}) = -\mu_0 \sum_{l=0}^{\infty} \sum_{m=-1}^l \beta_{lm} \nabla(r^l Y_{lm}(\theta, \phi)), \quad [5.27]$$

where β_{lm} are the coefficients that determine the contribution of each harmonic, and $Y_{lm}(\theta, \phi)$ are the spherical harmonic functions. Indices l and m are normally referred to as the order and degree of the spherical harmonic approximation, respectively. Finding which set of coefficients β_{lm} best describes the field measured by the OPM array within the central volume of the MSR can therefore help simulate the remnant background field. The problem can be cast as a matrix equation

$$\mathbf{b}_e = \mathbf{B}_{mat} \boldsymbol{\beta}, \quad [5.28]$$

where $\mathbf{b}_e$ is the measured field by a sensor pointing along its sensitive axis $\mathbf{e}$, $\boldsymbol{\beta}$ are the model coefficients and $\mathbf{B}_{mat}$ is the design matrix, which captures the spatial variation of a magnetic field of unit strength according to the spherical harmonics. The weights can then be found with

$$\boldsymbol{\beta} = \mathbf{B}_{mat}^{\dagger} \mathbf{b}_e, \quad [5.29]$$

where $\mathbf{B}_{mat}^{\dagger}$ is the pseudo-inverse of $\mathbf{B}_{mat}$.

l	m	$r^l S_{lm}$	$\frac{\partial(r^l S_{lm})}{\partial x}$	$\frac{\partial(r^l S_{lm})}{\partial y}$	$\frac{\partial(r^l S_{lm})}{\partial z}$
0	0	1	0	0	0
1	-1	y	0	1	0
	0	z	0	0	1
	1	x	1	0	0
2	-2	xy	y	x	0
	-1	yz	0	z	y
	0	$2z^2 - x^2 - y^2$	x	y	z
	1	zx	z	0	x
	2	$x^2 - y^2$	x	y	0
3	-3	$(3x^2 - y^2)y$	xy	$x^2 - y^2$	0
	-2	xyz	yz	xz	xy
	-1	$y(x^2 + y^2 - 4z^2)$	xy	$x^2 + 3y^2 - 4z^2$	zy
	0	$z(2z^2 - 3x^2 - 3y^2)$	xz	yz	$6z^2 - 3x^2 - 2y^2$
	1	$x(x^2 + y^2 - 4z^2)$	$2x^2 + y^2 - 4z^2$	xy	xz
	2	$(x^2 - y^2)z$	xz	yz	$x^2 - y^2$
	3	$(3y^2 - x^2)x$	$x^2 - y^2$	xy	0

Figure 5.11: Real-valued spherical harmonic functions up to the third order in Cartesian coordinates multiplied by r^l , where $\mathbf{r} = \sqrt{x^2 + y^2 + z^2}$. The multiplying constants have been removed for simplicity. The table includes the derivatives with respect to, x , y , and z , they represent the components of the displacement vector $\mathbf{r}$. Table adapted from Mellor et al., 2021.

A more practical perspective can help describe the physical meaning of equation 5.28. First, rotating a magnetometer around e_x , e_y , and e_z generates changes in the measured field due to the uniform field components. Translations and rotations of the sensor also induce changes in the measured field due to spatially dependent field gradient components. The matrix $\mathbf{B}_{mat}$ is based on the measured M channel positions and orientations at each of T time-points. The measured field column vector $\mathbf{b}_e$ contains the magnetic fields measured by each of the M sensor channels at the same T time-points. Therefore, $\mathbf{B}_{mat}$ has a column for each sensor and each magnetic field component. The number of magnetic field components is $(l - 1)^l$, which comes from the order of the spherical harmonics. The table in Figure 5.11 shows an example of low order spherical harmonics in cartesian coordinates used to estimate the design matrix $\mathbf{B}_{mat}$. This results in a very accurate model of the magnetic field over the volume of interest. The mapping can be achieved by recording magnetometer data while tracking the sensor's position. Once the coefficients are found, the field components are characterised. In the case of the bi-planar coils a second order spherical harmonic model can be used to estimate B_y , B_z , G_{xz} , G_{yz} , G_{zz} . This result can then be used to tune the voltages sent to the coil elements to produce an opposite field to $\mathbf{b}_e$.

5.3.2.4 Limitations

Thus far, this chapter has demonstrated how the combination of both passive and active shielding systems is key for OPM-MEG. This system architecture, however, can have some drawbacks. As discussed in the first chapter, the use of high permeability materials makes MSRs expensive and very heavy (~10 tons) to install. Alternative designs for MSRs could use cylindrical designs, which would improve shielding efficiency. On the other hand, this shield geometry would be impractical for MEG, potentially restricting

participant movement with the added problems of designing the access point and cable routing. Reducing the number of layers that make up the shield could also help reduce costs and weight. This solution however would require performance improvements of the sensors and active shielding systems.

Additionally, the use of a reference array placed near the participant may be impractical in some respects. The nulling performance seems to be slightly diminished for the OPM array in the helmet when compared to signals from the reference array (Holmes et al., 2018a). This is partly due to geometry of the array in the helmet and variations in the field in the space separating the reference array for the participant. Despite the small change in field reduction, the OPMs in the array always stay within their dynamic range (Holmes et al., 2018a).

The presence of both the reference sensors and coils near the participant may also introduce constraints on experimental design. The bi-planar coils were designed with a central target volume of $40 \times 40 \times 40 \text{ cm}^3$, which introduces limitations to participant movement and placement within the MSR. The fixed nulling volume does not allow for participants to stand up or move beyond this central region. Simultaneous scanning of two participants is also unviable with this setup. This could be solved by increasing the size of the target volume by designing the coils using larger panels.

A very promising alternative to planar coils is the use of multi-coil setups, similar to those developed for shimming in MRI (Gruetter, 1993; Juchem et al., 2010, 2011b). These systems, comprised of numerous smaller, individual coils, offer unprecedented versatility for magnetic field control in MEG applications. While Helmholtz or planar coil designs produce highly uniform fields, multi-coil arrays can synthesize more intricate field patterns through the superposition of fields from individual elements. The development of such a system for active shielding in OPM-MEG is discussed in Chapter 7.

Chapter 6 The role of beta bursts in top-down inhibition of somatosensory cortex: an OPM-MEG study

6.1 Abstract

In the somatosensory cortices, the dominant neural oscillations occur in the beta (13-30 Hz) band and are thought to mediate top-down inhibition of primary cortices. The non-invasive measurement of such oscillations has traditionally been made possible using either EEG or magnetoencephalography MEG. In this study, we utilised OPM-MEG to measure attentional modulation of beta oscillations in the somatosensory cortex. Using piezo-electric crystal stimulators, we presented ‘braille-like’ patterns to the left and right index fingers; participants were asked to respond to pre-specified target patterns presented to an attended hand, whilst ignoring patterns presented to their non-attended hand. This chapter covers the methodology and results obtained, demonstrating that beta amplitude significantly decreased during attended stimuli relative to baseline, and to non-attended stimuli, with the most pronounced effect during an attentional cue. Moreover, we extended our analyses to show that attention has a similar effect on the occurrence of pan-spectral bursts. My contributions to this work include study conceptualisation, methodology, software development, data acquisition, processing and visualisation. Additionally, I wrote and edited the contents of this chapter for submission to Scientific Reports, with the manuscript currently under peer review.

6.2 Introduction

As detailed in Chapter 2, neural oscillations play an important role in brain function, for example by coordinating spatially separate brain regions to promote efficient transfer of information (Fries, 2005). The precise functional role of these oscillations remains unclear; however, the amplitude of beta oscillations is robustly modulated by both sensory and motor tasks (Pfurtscheller and Lopes da Silva, 1999). Specifically, during motor output or sensory stimulation we observe a decrease in beta amplitude, followed by a ‘rebound’ (i.e. an increase above baseline) on movement (or stimulus) cessation. This has led to theories that high beta amplitude reflects top-down inhibition of primary sensorimotor cortices (see Barone and Rossiter, 2021, for a review). The importance of understanding these phenomena is underscored by studies showing that they appear abnormal in patients with a variety of neurological and psychiatric conditions; from disorders that strike in childhood (e.g. Autistic spectrum disorders (Ronconi et al., 2020)) to problems typically associated with older people (e.g. Parkinson’s disease (Little and Brown, 2014)). Developing a

better understanding of oscillatory dynamics is therefore not only critical to our understanding of brain function but could also shed significant light on how neural dysfunction affects brain health.

The “classical” view of beta oscillations is that they comprise a smooth continuous wave, whose amplitude changes during a task. However, recent studies (Jones, 2016; Little et al., 2019; Sherman et al., 2016; Shin et al., 2017) suggest that this is likely an effect of trial averaging. Briefly, when looking at unaveraged data, the beta band appears dominated by punctate ‘bursts’ of activity and the probability of burst occurrence modulates with a task (Little et al., 2019; Seedat et al., 2020). When averaged over many trials, a summation of bursts occurring at different times gives the appearance of a smooth oscillations, whose amplitude change in time. The rate and precise timing of beta bursts have been linked to behaviour and task performance metrics, such as reaction time (Diesburg et al., 2021; Echeverria-Altuna et al., 2022; Enz et al., 2021; Heideman et al., 2020; Howe et al., 2011; Karvat et al., 2020; Little et al., 2019; Sherman et al., 2016; Shin et al., 2017; Sporn et al., 2020). Recent studies further suggest that bursts characteristics change with age (from childhood to adulthood (Rayson et al., 2023; Rier et al., 2024)) and that bursts occurring during different phases of a task (e.g. before and after a movement) have different spectral, spatial and temporal properties, suggesting different functional roles (Szul et al., 2023; Zich et al., 2023). These insights have led to the development of biophysical models (Law et al., 2022; Neymotin et al., 2020; Sherman et al., 2016; Shin et al., 2017) with evidence suggesting that variability in burst morphology can be explained by variability of synaptic inputs to neural assemblies. In sum, these recent studies have resulted in a fundamentally new understanding of beta dynamics, their modulation by tasks, and their mechanism of generation.

Measurement of beta dynamics has been performed (non-invasively) using EEG or MEG. Although both offer a useful metric of electrophysiology, they still have their unique limitations. Chapter 1 outlined some of these shortcomings, such as EEG’s sensitivity to interference generated by non-neuronal sources such as muscles (Whitham et al., 2007). In contrast, MEG has higher spatial resolution and is also less susceptible to non-neuronal artifacts (Baillet, 2017; Boto et al., 2019; Seedat et al., 2023a). Despite these advantages, conventional MEG still has its drawbacks, as demonstrated in Chapter 2. Cryogenic MEG systems can be expensive, sensitive to subject motion and impractical in some cohorts. The requirement for thermal insulation limits sensor proximity and consequently sensitivity and spatial resolution.

Previously, we outlined how OPM-MEG can overcome some of these hurdles, hence providing an enhanced platform for measuring beta dynamics. OPMs do not require cryogenics, and can therefore be placed closer to the head (improving signal strength and spatial specificity) (Boto et al., 2017, 2016; Hill

et al., 2024; Iivanainen et al., 2017). In addition, OPM-MEG systems are wearable – adapting to head shape (Corvilain et al., 2023; Hill et al., 2019; Rier et al., 2024) and allowing movement during a scan (Holmes et al., 2018a, 2019a, 2023a). However, it is still a developing technology, predominantly showcased in technical demonstrations or comparisons with existing systems. There is relatively limited literature on employing OPM-MEG to address authentic neuroscientific challenges.

One striking finding using conventional MEG was the modulation of sensorimotor beta oscillations with attention. For example, in an early study by Markus Bauer et al., 2006, a sensory stimulator was used (an array of 8 ‘pins’, each individually controllable) to apply spatially different ‘braille-like’ patterns to either the left or right index fingers. Participants were asked to attend to a specific hand (left or right) and to respond if they felt a pre-specified ‘target’ stimulus. The findings revealed that beta amplitude modulation varied depending on the attended hand; for instance, when participants focused on their left index finger, beta amplitude decreased in the right sensory cortex. The reverse was true when participants attended to their right hand. These modulations were subtle, but added significant weight to an argument that beta oscillations provide top-down inhibitory influence on primary cortices. In this chapter, we design a similar experiment, with two goals: First, we aim to show that these subtle beta modulations with attention are measurable using OPM-MEG. Second, we aim to discover whether this attentional modulation in beta amplitude can be explained using the burst model of oscillatory dynamics.

6.3 Methods

6.3.1 Tactile attention paradigm

All participants gave written informed consent to take part in the experiment, which was approved by the University of Nottingham Faculty of Health Science Research Ethics Committee. The scanning procedure was performed following relevant guidelines for OPM-MEG. Consent and authorisation for publication of Figure 6.2B were also obtained. The experimental paradigm (Markus Bauer et al., 2006) involved tactile stimulation of the subject’s index fingers using braille stimulators (Metec, Germany). Each stimulator houses 8 pins arranged in a 4x2 matrix; each pin is controlled individually by a piezoelectric crystal which places them either up (stimulating) or down (not stimulating) when a voltage is applied. To control the voltage, we used an in-house developed electronics unit comprising a shift register and DC converter. This receives serial commands sent from a computer and translates these to a desired pattern of up and down pins on the braille cells. In this way, it is possible to present any spatial pattern of pins to the subject. The braille cells were controlled using the PsychoPy library (Peirce et al., 2019). All code used to control the task is available on GitHub (github.com/GonReina).

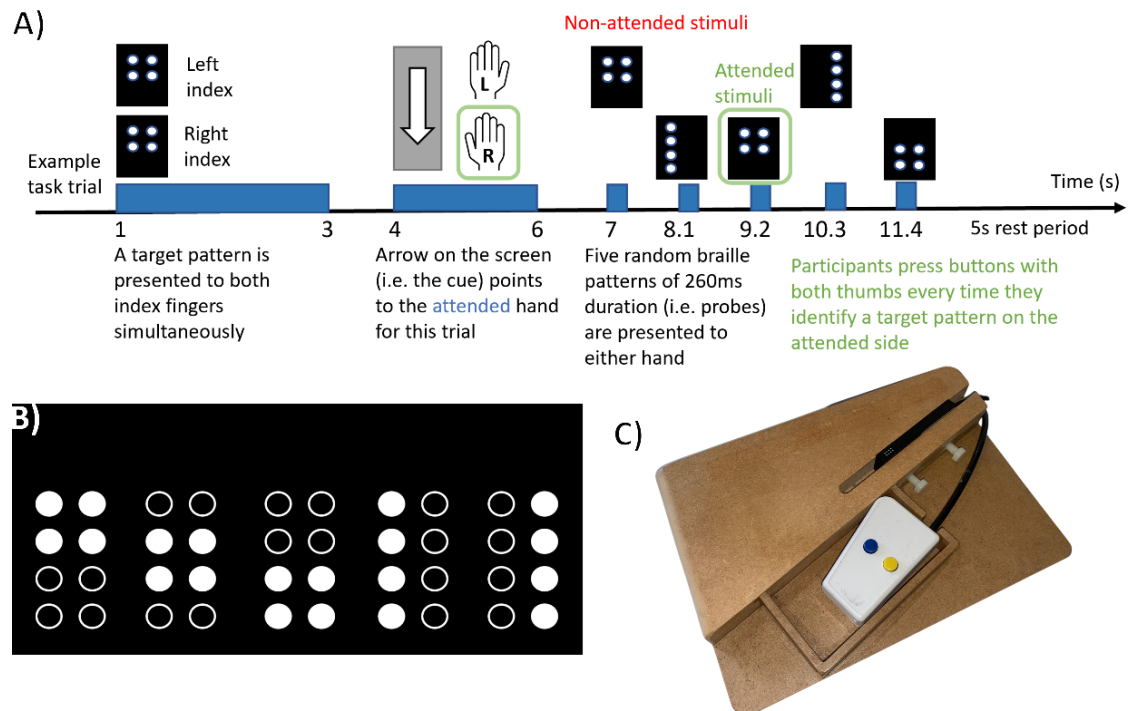


Figure 6.1: Tactile attention task. *A) Schematic diagram of the braille attention task for a single trial. B) The five different braille patterns used during the experiment: all patterns have 4 pins up (white dots) and 4 pins down (black dots). C) Wooden mount used to hold the braille stimulators and response buttons. The hand is placed such that the index finger is over the braille pins, and the blue button can be accessed by the thumb.*

A schematic of the experiment is shown in Figure 6.1A. A single trial lasts 16 s. In the $1\text{ s} < t < 3\text{ s}$ time window, a target pattern is presented to both left and right index fingers. Following this, in the $4\text{ s} < t < 6\text{ s}$ window a visual cue (an arrow pointing either left or right) is shown on a screen; this directs the subject to the attended hand. 5 ‘probe stimuli’ are then applied pseudo-randomly to either the left or right fingers (the first at $t = 7\text{ s}$, and then at intervals of 1.1 s. Each stimulus lasts 260 ms). Participants were instructed to respond via a MEG compatible response box (Current designs Inc., Philadelphia, PA) by pressing a button with both thumbs (regardless of which hand the probe was felt on) if a probe stimulus matched the target pattern on the attended hand. To simplify the experiment, we limited ourselves to 5 spatial patterns, which are shown in Figure 6.1B. The target pattern was picked at random at the start of each trial. The probability of the target pattern being presented on the attended hand was 10%. The cues indicating the attended hand were pseudorandomised, with half of the trials cueing the left hand and the other half, the right hand. The stimulators were held in place along with the response buttons by custom-made wooden supports (Figure 6.1C). Signals were sent from the computer controlling the braille stimulators to the OPM-MEG acquisition system to delineate the timing of each event in the paradigm (henceforth termed triggers). 80 trials were recorded, along with a rest trial every 10 trials, showing feedback to the participants on their performance. Performance was calculated by taking the number of correct

button presses as a fraction of the total number of presses. The total experimental length was 1408 s.

6.3.2 OPM-MEG system overview

All data were collected using an OPM-MEG system at the University of Nottingham (Boto et al., 2022; Rea et al., 2022; Rhodes et al., 2023) (see Figure 6.2A for a schematic). Participants sat in front of the screen, at the centre of a magnetically shielded room (MuRoom, Magnetic Shields Ltd., Kent, UK) with their hands resting on the wooden supports (Figure 6.2B). The non-magnetic chair was placed at the isocentre of a set of bi-planar electromagnetic coils, which were used to control background magnetic fields (Cerca Magnetix Ltd., Nottingham, UK).

As detailed in Chapter 3, MEG data were collected using an array of 3rd generation, triaxial, zero-field OPMs (QuSpin Inc. Louisville, CO, USA). These were mounted in 3D-printed helmets of varying size (Cerca Magnetix Ltd.) and gave approximate whole head coverage (Figure 6.2B). The sensor array was connected to a National Instruments (NI, Austin, Texas, USA) Data Acquisition Unit (DAQ) (NI-cDAQ-9179) which captured the signals from all channels, alongside the stimulus triggers, at a sample rate of 1,200 Hz with 16-bit precision. The OPMs were controlled by a single acquisition PC using serial commands via the (manufacturer provided) OPM control software; this was used to set up and calibrate the OPMs at the start of every recording. The same (acquisition) PC was also used to control the bi-planar coils to compensate background fields. A separate (stimulus) PC was used to control the experimental paradigm. Visual stimuli were presented via back-projection through a waveguide in the MSR and onto a screen located ~1 m in front of the subject. We used a ViewSonic PX748-4K projector. A system of 6 motion tracking cameras (OptiTrack Flex 13, NaturalPoint Inc., Corvallis, Oregon, USA) was also available to track motion of infra-red retroreflective markers, which were attached to the helmet. This allowed real-time head motion tracking. Following the techniques described in Chapter 5, background magnetic fields were compensated using bi-planar coils, informed by signals obtained with a second OPM array, comprising 4 dual axis OPMs (QuSpin, 1st generation) placed behind the subject.

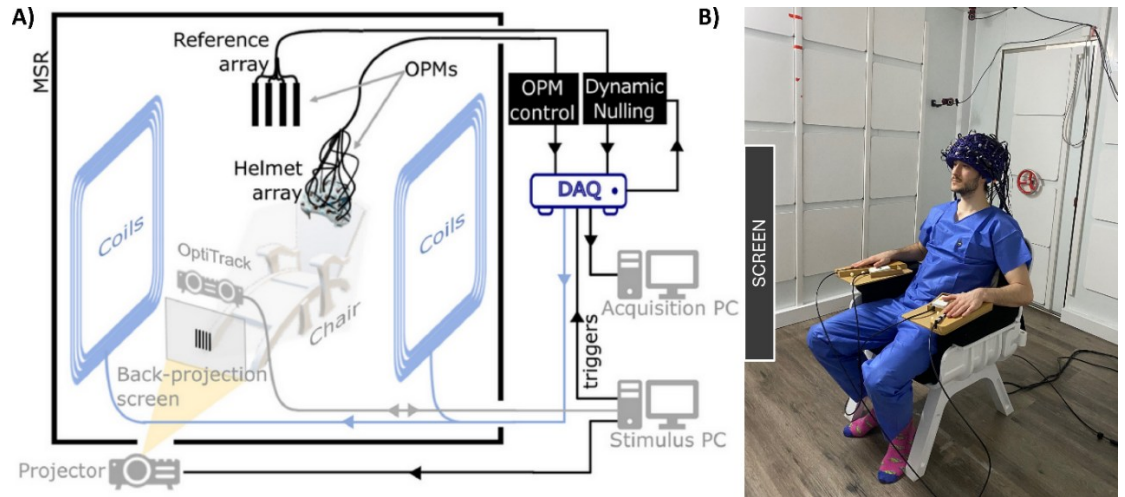


Figure 6.2: OPM-MEG system. A) Schematic of the OPM-MEG system. Figure adapted from Hill et al., 2022. B) Photograph of a subject completing the task (consent and authorisation for publication was obtained).

As a consequence of using a novel system, the setup changed over time, often being subject to maintenance, upgrades and alterations. This meant that some subjects were scanned with a different number of channels in the array. Initially, 9 subjects were scanned using a 132-channel array. A second set of scans, in 15 subjects (6 of whom had been scanned previously) was then performed using a 192-channel array. This yielded a total of 24 datasets from 18 participants. Appendix I shows an investigation into the impact of the variation in channel counts on our analysis, which was found to be minimal in the brain regions of interest (somatosensory cortices). To avoid conflation of inter- and intra-subject variance, in our final analyses only one scan per subject (that with the higher channel count) was used.

6.3.3 Background magnetic field control

The magnetic field inside the MSR was controlled using a 3-step process, carried out for every scan. Firstly, the inner mu-metal walls of the MSR were demagnetised using a degaussing procedure as described in Section 5.2.5 (Altarev et al., 2015), resulting in a drop in magnetic field magnitude from ~ 8 nT to ~ 2 nT. Following this, dynamic field compensation was applied, using the reference array to measure change in background field over time and the bi-planar coils to compensate for any measured drift. Once enabled, this ensured a temporally stable (but non-zero) background field. Finally, we employed the field mapping and compensation technique described in Section 5.3.2.3 to remove the remaining static field (Mellor et al., 2022; Rea et al., 2021a). Briefly, participants performed a series of head movements during which changes in magnetic field at the OPMs were recorded alongside synchronised head motion data. These data were then fitted to a spherical harmonic model of magnetic fields across the volume occupied by the helmet, to estimate the strength and

spatial variation of the field. An equal and opposite (DC) field was then generated by the bi-planar coils. This nulling process reduces remnant static background magnetic field to ~ 0.3 nT and ensures accurate data are recorded with minimal motion artefact (Rhodes et al., 2023).

6.3.4 Co-registration

MEG data can be mathematically modelled to create 3D volumetric images, showing moment-to-moment changes in brain electrophysiology. As established in Chapter 4, this process requires accurate knowledge of the OPM locations and orientations with respect to the brain anatomy. To achieve this, we used an optical technique (Hill et al., 2020; Zetter et al., 2019). Immediately prior to MEG data acquisition, two 3-dimensional optical scans of the subject's head were acquired. In the first scan, the subject was asked to wear a swimming cap (to flatten their hair); this was used to get an approximation to head shape. In the second scan, the subject was scanned with the OPM-MEG helmet in position; this measured the location of the helmet relative to the face. In both cases data were obtained using either a Skanect (Occipital Inc., San Francisco, CA, USA) infrared structured light scanner (for the first set of 9 subjects) or a 3D structured light scan (Einscan H, SHINING 3D, Hangzhou, China) (for the second set of 15 subjects). The resulting 3D meshes of the subject's face/head were aligned with each other using Meshlab (Cignoni et al., 2008). The scan with the helmet was combined with knowledge of sensor geometry inside the helmet (from the helmet 3D-printing process) to delineate the sensor locations and orientations relative to the face and scalp. Finally, every subject had previously undergone a T_1 weighted anatomical MRI scan (3T Phillips Ingenia; MPAGE sequence; 1 mm isotropic resolution). By extracting the scalp surface from the MRI and fitting it to the optical digitisation of the head, we enabled complete co-registration of the sensor locations/orientations to brain anatomy.

6.3.5 Data Pre-processing

All datasets (including co-registration information) were organised according to the Brain Imaging Data Structure (BIDS) guidelines (Gorgolewski et al., 2016). Data pre-processing was carried out using a pipeline developed in-house and implemented in MATLAB. First, power spectral density (PSD) measures for all channels were generated using Welch's method (Gramfort et al., 2013; Welch, 1967). This approach involves dividing the recording into segments and then averaging adjusted periodograms of these segments. PSD results were inspected to ensure there were no major artifacts in the data. This led to the removal of two datasets: the first due to noisy signals caused by a power supply fault, and the second due to missing data caused by a problem with the acquisition software. This left a total of 22 usable datasets from 16 participants. (Of the remaining subjects, 14 were right-handed; 8 identified as male, 8 female; the average subject age was 27.4 ± 3.2 .) Bad channels were

visually identified by plotting both the channel time course and the PSD (using MNE-python (Gramfort et al., 2013)). Any channels with excess noise (above ~ 16 fT/sqrt(Hz) in the 5-150 Hz range) or a PSD of zero were removed. Following this, data were segmented into trials. To eliminate bad trials, a standard deviation threshold was identified by combining data across all trials, calculating the mean and standard deviation, and then computing the standard deviation values for each trial individually. Any individual trial (including rest blocks) with a standard deviation value exceeding three times that of the combined data was removed. Following this, homogeneous field correction was performed to attenuate the effects of interference that manifests as spatially uniform magnetic field changes across the sensor array (as such uniform fields are unlikely to represent brain activity) (Tierney et al., 2021).

6.3.6 Source space analysis

For source space analysis, the brain was parcellated into 78 cortical regions, defined by the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). This was achieved by warping a template brain to each individual's anatomy using FSL's FLIRT tool (Jenkinson et al., 2002a; Jenkinson and Smith, 2001) and applying the same transform to the AAL atlas. First, source positions were located at the centre of mass of each AAL region. Using the spatial filtering technique previously described (Section 4.8), sensor signals were projected to these source locations via a linearly constrained minimum variance (LCMV) scalar beamformer (Van Veen et al., 1997). As described in Chapter 4, forward solutions were calculated based on a current dipole and a single shell volume conductor model (Guido Nolte, 2003) using Fieldtrip (Oostenveld et al., 2010). Covariance matrices were computed separately for distinct frequency bands of interest, including broad-band (1-48 Hz) and beta-band (13-30 Hz). These matrices were regularised using the Tikhonov method with a regularisation parameter equal to 5% of the maximum eigenvalue of the unregularized covariance matrix (Brookes et al., 2008). Beamformer reconstructions of the timecourse of electrophysiological activity (termed virtual electrodes) were constructed for each region, and separately in each frequency band. The result was both a broadband and beta band virtual electrode timecourse for each of the 78 brain regions, in each of the 16 subjects.

6.3.6.1 Beta Envelopes

For each brain region, we estimated instantaneous task induced contrast to noise ratio (CNR) in the beta band as a measure of change in beta amplitude. Beta filtered data from the whole experiment were Hilbert transformed to generate the analytic signal; the absolute value of this provided the 'Hilbert envelope' which shows the instantaneous oscillatory amplitude as a function of time. Following this, two separate analyses were carried out relative to both the 16 second trials and the individual probe stimuli:

- **Trials:** Data were segmented into 16-s trials, which were split into two groups – attend left and attend right. Baseline mean and standard deviation were estimated based on the last 8 seconds of the interspersed rest trials (I.e. baseline was recorded in a window that started at least 15 seconds after the last stimulus was presented). Envelope data for all trials were averaged within each group, baseline corrected (by subtracting the mean beta amplitude in the rest trials) and normalised (by dividing by the standard deviation of the rest trials). This resulted in an instantaneous CNR timecourse reflecting the change in beta envelope from baseline as a percentage of standard deviation of the baseline.
- **Probe stimuli:** Data were also segmented into time windows from -180 ms to +650 ms relative to the probe stimuli. There were 4 categories of probe: attend left stimulate left; attend left stimulate right; attend right stimulate left; attend right stimulate right). We averaged envelope signals for each type of probe stimulus and again baseline corrected and normalised (using the rest trials). We removed target stimuli (which only occur for attended stimuli) from the analysis, and this necessarily led to having more non-attended than attended trials. This difference was addressed by removing randomly selected probes to equalise the trial counts.

All calculations were performed separately for every subject, and data were averaged across subjects for the final analyses.

6.3.6.2 Burst analysis

We used a univariate time delay embedded HMM, applied to the 1-48 Hz virtual electrode data, to identify pan-spectral bursts. As discussed in Section 4.11.2, this method has been described extensively in previous papers (Gascoyne et al., 2020; Rier et al., 2021; Seedat et al., 2023b, 2020); a more detailed mathematical description can also be found (Baker et al., 2014; Vidaurre et al., 2018). Briefly, we took the virtual electrode time series and used the HMM to identify the occurrence of three “states” each depicting repeating patterns of activity with similar temporo-spectral signatures. The output was three timecourses representing the likelihood of each state being active as a function of time. These were binarized (using a threshold of 2/3) to provide a timecourse of state occurrence. Note that the Markovian property means that the likelihood of state occurrence is dependent only on the previous state; states are mutually exclusive and all time points in the virtual electrode timecourse must belong to one of the three states. The state whose timecourse correlated highest with the beta envelope was defined as the “burst state”. This approach to burst identification presents some advantages over more traditional approaches (which usually involve spectral filtering to the beta band and thresholding beta amplitude). First, it eliminates the underlying assumption that bursts are exclusively generated by the beta band. Moreover, the use of broadband-filtered data and time embedding enables characterisation of the spectral properties of the bursts. (For this, we used a state-wise multi-taper analysis method, developed

in existing work (Vidaurre et al., 2016)). Unfortunately, one subject was excluded from the analyses due to an inadequate fit by the HMM.

The binarised burst timecourses were taken for each trial and, for each time point within a trial, we measured the statistical likelihood of burst occurrence. This was computed as the number of trials with a burst at that time point, divided by the total number of trials. Timecourses of burst probability were constructed for both trial types (attend left and attend right). In addition, we measured burst probability (in the same way) for the four probe types (attend left stimulate left; attend left stimulate right; attend right stimulate left; attend right stimulate right).

6.3.7 Statistical analyses

Our primary hypothesis was that, using OPM-MEG, we would observe attentional modulation of beta amplitude. To this end, we undertook three sets of statistical analyses.

- 1) **Beta modulation by attentional cue:** We averaged beta amplitude across the time window when the attentional cue was presented (i.e. $4\text{ s} < t < 6\text{ s}$ relative to trial start). We then conducted two statistical tests. First, looking in left sensory cortex (where we expect the largest activity for right-hand stimulation), we contrasted right-cued (attended) versus left-cued (non-attended) trials. We predicted lower beta amplitude following an attended cue. Second, looking in right sensory cortex (largest activity for left-hand stimulation) we again contrasted right-cued (non-attended) versus left-cued (attended) trials, predicting lower beta amplitude following an attended cue. In all cases, beta amplitudes were averaged over trials for each subject, and statistical significance was assessed across subjects using a non-parametric Wilcoxon sign-rank test.
- 2) **Beta modulation during probe stimuli.** Beta amplitude was averaged in the $0\text{ ms} < t < 260\text{ ms}$ window relative to the presentation of probe stimuli. (All target stimuli, or stimuli where a button was incorrectly pressed, were excluded from these analyses to remove confounds of the button press and the number of attended/non-attended stimuli were equalised as detailed above.) We conducted two statistical tests. First, we looked in left sensory cortex following probe stimuli presented to the right hand, and contrasted beta amplitude when subjects were attending to their left (non-attended) or right (attended) hand. We expected smaller beta amplitude when the right hand was attended. Second, we looked in right sensory cortex following a left-handed probe and again contrasted beta amplitude with attention. Here, we expected smaller beta amplitude when the lefthand was attended. Significance was assessed using a Wilcoxon sign-rank test.

In total, for the above analyses we conducted 4 statistical tests. Multiple comparisons were controlled using the Benjamini-Hochberg method and we set the false discovery rate to 5%.

Our second hypothesis was that any measurable effect of attention on beta amplitude would be mirrored by a change in the dynamics of pan-spectral bursts. To test this, we conducted the same tests as those described above, but using burst probability timecourses derived using the HMM (rather than beta envelope). This allowed us to test whether there were significant changes in burst probability with attentional shift. However, a change in burst probability could be driven by either an increase in the number of bursts per unit time (burst count) or by a change in burst duration. Similarly, a change in beta envelope could result from altered burst count, duration, or amplitude. We therefore derived three additional burst-related metrics:

- 1) **Burst count:** The number of bursts occurring within a time window. Note, bursts were only counted if they were fully encapsulated (i.e. started and ended) within the window of interest.
- 2) **Burst duration:** Defined as the length of time (for a single burst) that the binary time series delineating the burst state was set to 1 by the HMM binarization.
- 3) **Burst amplitude:** We took the 1-48 Hz timeseries (on which the HMM was based), computed the Hilbert envelope (as above) and found the maximum amplitude during each burst.

These three measurements were made on all bursts occurring during presentation of the attentional cues ($4\text{ s} < t < 6\text{ s}$ relative to trial start) and during the window around probe stimuli ($0\text{ s} < t < 1.1\text{ s}$ relative to the probe onset). In the former case we contrasted left and right attentional cues and measured the difference in count, amplitude and duration. In the latter case we contrasted attended and non-attended probes (and measured the same differences). In all cases, measures were derived in left and right somatosensory cortices independently and statistical significance was assessed using a Wilcoxon sign-rank test. This resulted in 12 separate statistical tests (3 metrics x 2 windows x 2 brain regions). Multiple comparisons were again controlled using the Benjamini-Hochberg method.

6.4 Results

In general subjects found the task difficult. The overall accuracy (defined as the number of correct button responses (i.e. button presses following a target) divided by the total number of times a subject made a button press) was $51.25 \pm 20.51\%$ (mean $\pm$ standard deviation over all subjects). Accuracy was also calculated independently for left-cued and right cued trials, but we found no significant difference between them. Accuracy was also measured in the first

third, and last third of trials, to test for a learning effect, however we again found no significant difference.

6.4.1 Beta band amplitude modulates with attention

Figure 6.3A shows the spatial signature of instantaneous beta band envelope (CNR), at a time point ~300 ms following presentation of a probe stimulus. (This is the median time at which CNR showed the largest difference from baseline across all conditions). The left and right sub-panels show stimulation to the left and right hands, respectively. The upper- and lower-sub-panels show attended and non-attended stimuli. As expected, the postcentral gyri (primary sensory cortices) exhibited the highest CNR, with left hemisphere dominant for probes presented to the right hand, and vice versa. There were no measurable spatial differences (at the scale of the AAL brain parcellation) for attended and non-attended stimuli.

Figure 6.3B shows beta envelope timecourses throughout a trial. The upper plot shows the envelope for the left somatosensory cortex and the lower plot shows the equivalent for the right somatosensory cortex. In both cases, the orange trace shows right-cued trials and the purple trace shows left-cued trials. The shaded areas depict standard error on the mean across subjects. The data show clearly that sensory stimulation produced a marked drop (of around 100 %) in beta amplitude relative to baseline, as expected; this is clear for both the target stimulus (shown by the purple shaded area) and probe stimuli (shown by the green shaded areas). Throughout the start of a trial, the presentation of the target stimuli, and towards the end of the trial, beta envelopes for left- and right-cued trials are very similar (no effect of attention). However immediately following presentation of the attentional cue, and during the probe stimuli, they appear to diverge.

Statistical analysis showed that for both hemispheres, there was a significant difference following presentation of the attentional cue (the 4 s to 6 s window) suggesting beta envelope modulation by attention. Specifically, in left sensory cortex, right cued trials (i.e. attention directed to the relevant hand) resulted in significantly lower beta envelope following the cue ($p = 0.0053^*$; Wilcoxon sign-rank test - * indicates the effect remains significant following multiple comparison correction)). Similarly, in right sensory cortex, left cued trials resulted in significantly lower beta amplitude ($p = 0.00006^*$; Wilcoxon sign-rank test). This confirms the hypothesis that, using OPM-MEG, we were able to measure attentional modulation of beta amplitude – similar to that detected previously in conventional MEG (Markus Bauer et al., 2006).

A more in-depth analysis on the attentional cue (which was not part of our initial hypothesis) also showed that, in the 4-6 s time window, in the left sensory cortex with a left cue, beta amplitude wasn't significantly different to baseline (i.e. not shifted from zero in the plot) ($p = 0.72$; Wilcoxon Sign rank test) whereas with a right cue the beta amplitude decreased from baseline ($p = 0.0067$; Wilcoxon Sign rank test). Similarly in the right hemisphere, with a right cue beta amplitude wasn't significantly different to baseline ($p = 0.60$; Wilcoxon Sign rank test) whereas with a left cue the beta amplitude decreased from baseline ($p = 0.0067$; Wilcoxon Sign rank test). In other words, even in the absence of tactile stimulation a sensory cue produces a significant drop in beta amplitude in sensory cortex, if the cue points to the contralateral hand; a cue to the ipsilateral hand produces no significant effect.

Figure 6.3C shows the beta envelope following probe stimuli. The left-hand plot shows data for the left somatosensory cortex and the right-hand plot shows the right somatosensory cortex. In both cases, the orange trace shows attended and the purple trace non-attended stimuli; again, the shaded area represents standard error over subjects. The beta amplitude during presentation of attended stimuli is generally lower throughout the whole window (0 s to + 1.1s relative to the probe presentation; $p = 0.018^*$ in left sensory cortex and $p = 0.0215^*$ in right sensory cortex). Post hoc analysis of separate time windows during and after stimulation showed that beta envelopes have approximately the same amplitude during stimulation (0 ms to 260 ms; $p = 0.49$ for left sensory cortex $p = 0.022$ for right sensory cortex). With a significant decrease in amplitude for attended cases in a time window following stimulus offset – though this was only in the left sensory cortex (260 ms to 840 ms; $p = 0.0084$).

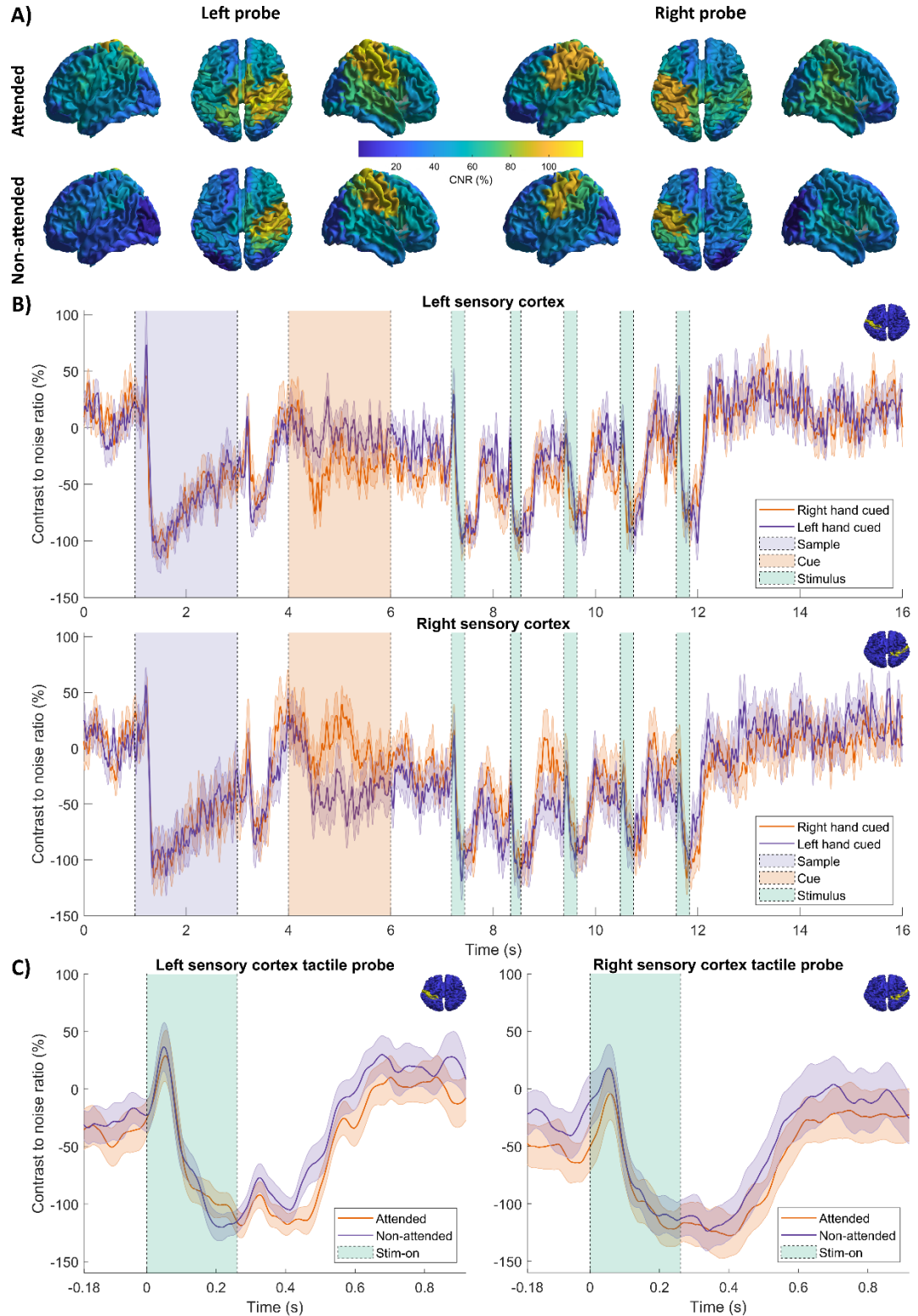


Figure 6.3: Beta CNR changes with attention: **A)** Colourmaps show beta CNR measured 300 ms after the onset of the probe stimulus. This point in time was selected as the largest deflection in the beta envelope from baseline on average between conditions in the somatosensory cortices. The top left panel show attend left, left hand probe; top right panel is attend right, right hand probe; bottom left panel is attend right, left hand probe and bottom right panel is attend left, right hand probe. **B)** Beta CNR timecourses for the 16 second trial. Panel i shows left somatosensory cortex; panel ii shows right somatosensory cortex. In both cases orange and

purple trace show trial averaged beta CNR for right and left cued trials, respectively. The shaded areas show standard error on the mean across subjects. **C)** Beta CNR timecourses following presentation of a probe stimulus. **i)** Left Somatosensory cortex. **ii)** Right somatosensory cortex. Here the orange and purple timecourses represent attended and non-attended probes.

6.4.2 Pan-spectral burst probability modulates with attention

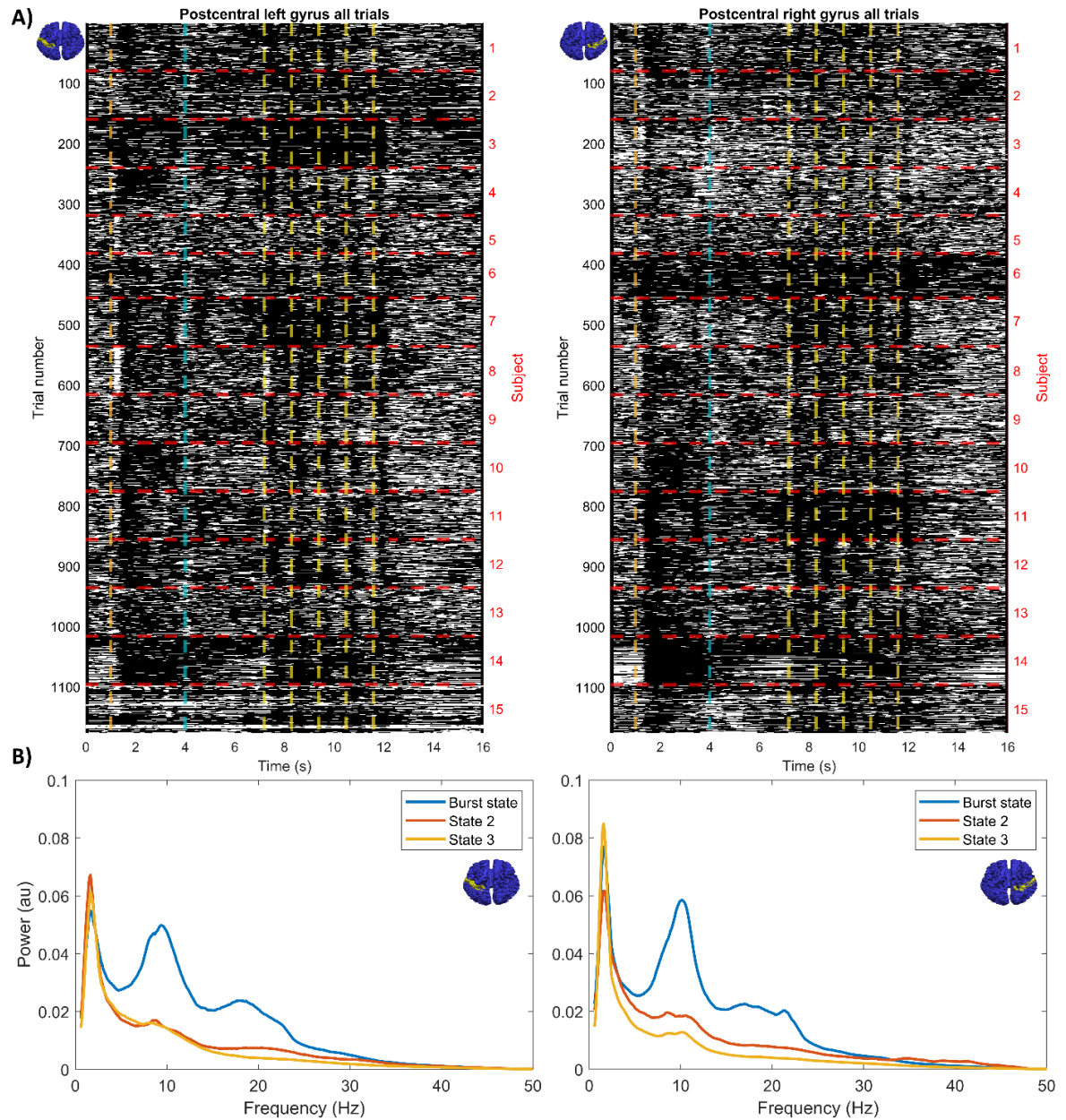


Figure 6.4: Pan spectral bursts during the task: A) Raster plots showing the binary timecourse of the burst state for all trials. Trials are concatenated in the y-axis. The x-axis represents time. White indicates presence of a burst, whereas black delineates the absence of a burst. Left panel shows the left somatosensory cortex, and right panel shows the right. **B)** Power spectral density plots for the three HMM states; the blue trace shows the burst state. Again, left and right panels respectively correspond to the left and right somatosensory cortices.

Figure 6.4A shows a raster-plot of burst occurrence in individual experimental trials. Panel i shows data for left sensory cortex, and panel ii shows right sensory cortex. In both cases, white indicates occurrence of a burst; black the absence of a burst. All trials for all subjects are concatenated in the y-axis. The onset of the target pattern, attentional cue and probe stimuli are shown with the dashed vertical lines; dashed horizontal lines delineate subjects. Note that the task structure can be seen clearly in these single trial data, with bursts less likely following sensory stimulation (both the target and the probes). It is also noteworthy that the burst structure changes markedly between subjects. Figure 6.4B shows power spectral density for each of the three states found by the HMM. Left and right somatosensory cortices are shown in the left and right plots respectively, and in both cases the burst state is shown in blue. Notice the pan-spectral nature of the bursts, with components not only in beta band but also at lower frequencies.

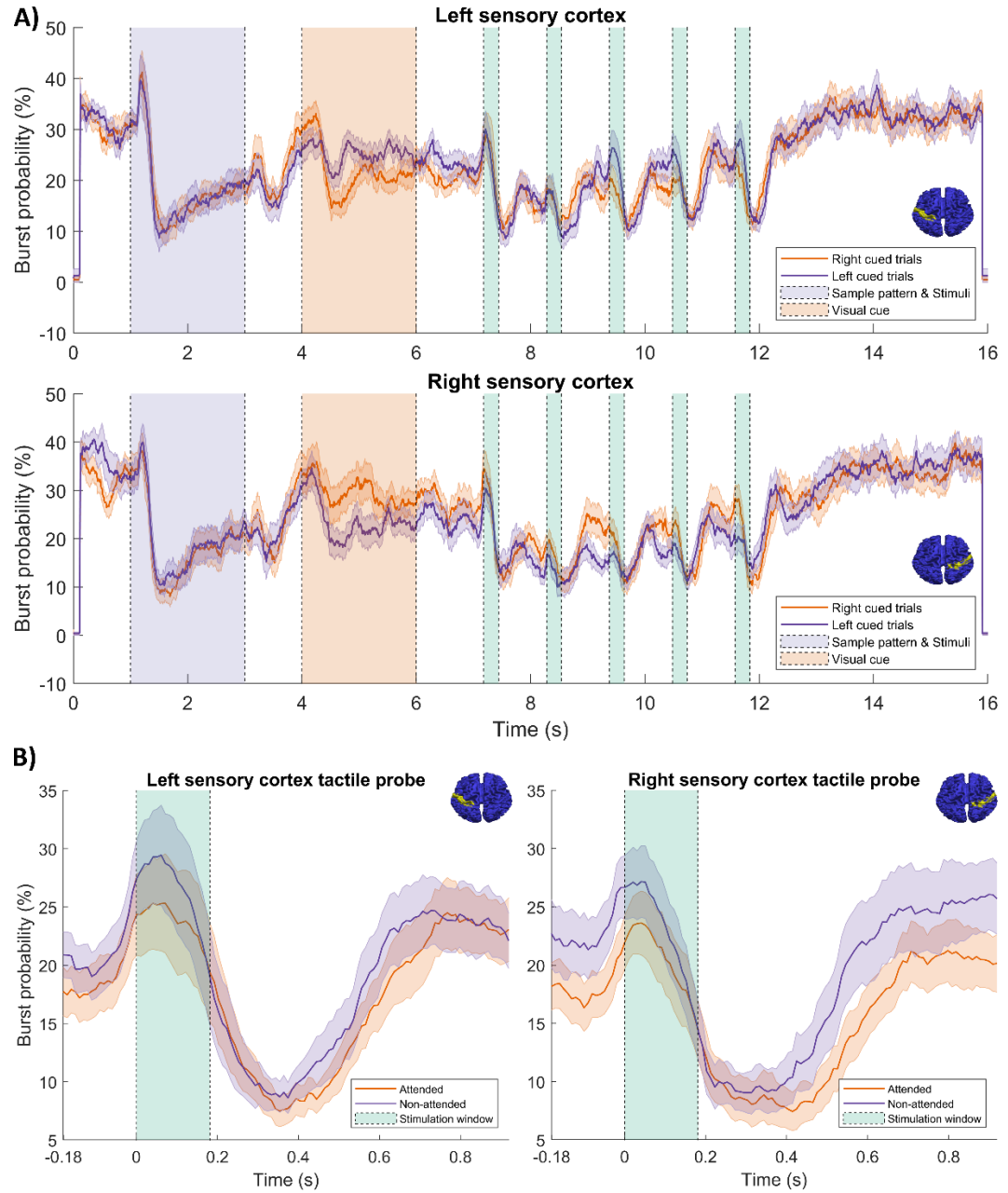


Figure 6.5: Modulation of pan-spectral burst probabilities by the task: *A)* Burst probability for the whole trial. Panel i shows left somatosensory cortex; panel ii shows right somatosensory cortex. The orange and purple traces show burst probability for right and left cued trials, respectively. The shaded areas show standard error across subjects. *B)* Burst probability following presentation of a probe stimulus. *i)* Right Somatosensory cortex. *ii)* Left somatosensory cortex. Here the orange and purple timecourses represent attended and unattended probes.

Figure 6.5 shows how the probability of bursts modulates throughout the task. Changes in burst probability during whole trials are shown in Figure 6.5A. The upper plot shows left somatosensory cortex, and the lower plot shows the right somatosensory cortex. The orange traces show right-cued trials, and the purple traces show left-cued trials. Sensory stimulation produced a drop (of ~20 %) in burst probability. Throughout the start of a trial and the presentation of the

target stimuli, burst probability for left- and right-cued trials is similar in both hemispheres, but the two diverge following presentation of the attentional cue. Specifically, there was a significant difference between left and right cue in the 4 s to 6 s time window: (in left hemisphere; $p = 0.0083^*$; in right hemisphere $p = 0.0006^*$). Figure 6.5B shows burst probability following probe stimuli. The left and right plots show results for the left and right somatosensory cortices respectively; for both, orange shows attended and purple non-attended stimuli. In both hemispheres, post-stimulus burst probability was slightly higher in the non-attended case, but this only reached significance in the right hemisphere (time window 260 ms to 840 ms; $p = 0.0181^*$).

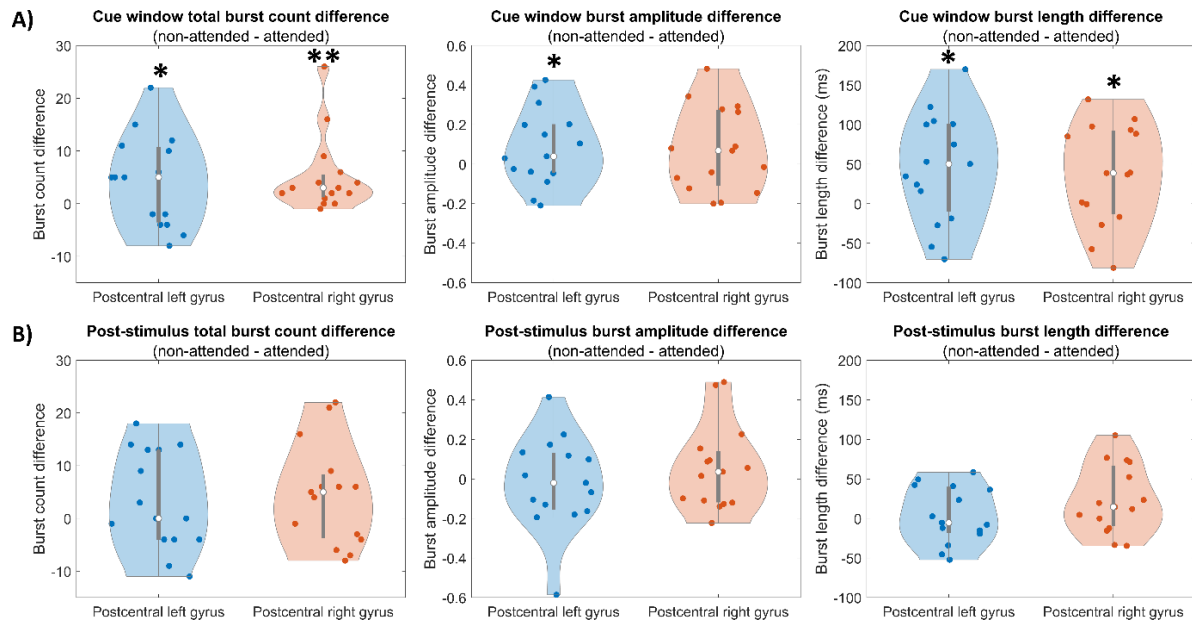


Figure 6.6: Burst statistics: The left, centre and right column show measurements of attentional differences in burst count, burst amplitude, and burst duration, respectively. In all cases, the top plot **A**) shows the difference between left and right attentional cues (bursts in the 0 s to 2 s window relative to the onset of an attentional cue). The bottom plot **B**) shows attended and non-attended probes (bursts in the 260 ms to 840 ms window relative to presentation of a probe). In all cases, data for the left (blue) and right (red) hemispheres are shown. Measurements show a significant effect of attention if they differ significantly from zero (** denotes significance following multiple comparison correction; * denotes a p -value < 0.05 uncorrected).

Finally, Figure 6.6 shows how burst count, amplitude and duration are modulated by attention. In the top row, we plot the difference between left and right attentional cues in the 0 s to 2 s window following cue onset. Note that in the plots, a “meaningful” attentional effect occurs for a pattern of results that differs significantly from zero. In right sensory cortex, burst count was significantly higher following a right (non-attended) cue compared to a left (attended) cue ($p = 0.0007$). There was also a trend towards a longer burst length ($p = 0.048$) during the cue, though this didn’t survive multiple comparison correction. In left sensory cortex there was a trend showing higher burst count following a left (non-attended) compared to right (attended) cue ($p = 0.04$). There were also trends towards higher burst amplitude ($p = 0.025$) and longer

duration ($p = 0.012$) following non-attended cues. However, none of these effects were significant following multiple comparison correction. In the time windows around the probe stimuli we saw no significant effects.

6.5 Discussion

As outlined in the third chapter, OPM-MEG has significant potential as a research and clinical tool. It offers a possible replacement for conventional MEG and an alternative to EEG – particularly in applications where high spatial specificity is important. Nevertheless, OPM-MEG remains new technology and its future adoption relies critically on demonstrations of utility within an array of neuroscientific and clinical use cases. Here, we have shown that OPM-MEG can be used to detect modulation of beta oscillations with changing attention. In our study, the sensory stimulus itself generated a $\sim 100\%$ dip in beta band amplitude post-stimulation (measured as a signal change relative to baseline standard deviation). This is typical of the types of signals that have been measured in OPM-MEG demonstrations to date, which most often comprise either evoked responses (Alem et al., 2023; Boto et al., 2017) or induced oscillatory modulation (Boto et al., 2018; Rea et al., 2022) elicited by simple paradigms. Here, the attentional modulation of the beta signal induced a $\sim 20\%$ change during the attentional cue window, for the left and right somatosensory cortices respectively (See Figure 6.3). The fact that this relatively subtle modulation, which has been observed previously using conventional MEG measurements (Markus Bauer et al., 2006), can be reliably measured provides evidence of the high-fidelity MEG metrics that are now afforded by OPM-MEG systems.

The scanner design itself warrants discussion. We employed triaxial OPM sensors (Shah et al., 2020) in an array design that has been well characterised by previous papers (Boto et al., 2022; Brookes et al., 2021; Rea et al., 2022; Rhodes et al., 2023). This design has significant advantages (over single or dual-axis OPM variants (Hill et al., 2020)) including better differentiation between signals originating inside and outside the brain (Brookes et al., 2021; Tierney et al., 2021), more homogeneous coverage of the cortex (Boto et al., 2022) and larger overall signal capture (Hill et al., 2024). However it does come at the cost of a slightly higher sensor noise floor (Boto et al., 2022). In addition, we employed background field control (Rea et al., 2021a; Rhodes et al., 2023) based on bi-planar coil technology, as described in Chapter 5 (Holmes et al., 2018a, 2019a). This enabled viable OPM operation in the presence of subject movement. Consequently, our subjects were not constrained to a helmet as would be the case for conventional MEG or some nascent OPM systems. However, a limitation in this study was that the experimental nature of the system meant that not all sensors were available for every scan, and consequently the channel count was different for different subjects. To mitigate this, we always tried to populate the sensor slots in the helmet to provide good coverage of the sensorimotor cortices, minimising the impact of sensor counts

changes. In addition, because we contrasted conditions within the same experiment (rather than conditions between subject groups) the effect of changing sensor count between subjects should be minimised (see Appendix I: Array formation variations). Nevertheless, in a subset of subjects, coverage was compromised, and this would make some types of analysis (e.g. whole-brain connectivity) challenging.

From a neuroscientific point of view, the observation of decreased beta amplitude during the presentation of attended stimuli supports the idea that the beta rhythm carries a top-down influence which helps to inhibit primary cortical areas. Interestingly, the most pronounced effects were during the attentional cue – i.e. in a window where no direct sensory stimulation was taking place. In this window, a cue directing attention to the ipsilateral hand caused no significant change in beta amplitude from baseline. However, a cue directing attention to the contralateral hand saw a significant drop in beta amplitude, making it tempting to speculate that role of this drop is to release top-down inhibition and enhancing excitability. In addition to the attentional cue, beta band amplitude was also significantly diminished during presentation of attended compared to non-attended stimuli – an effect most prominent before and after, but not actually during tactile stimulation (where it is likely masked by the sensory response itself).

Our analyses also suggest that the observed beta effects are (at least in part) driven by pan spectral bursts, which occur across a relatively large frequency range, though contain a prominent beta component (see Figure 6.4B). Our time-delay-embedded HMM detects repeating patterns of broadband (1-48 Hz) electrophysiological activity with a similar spectro-temporal profile (Vidaurre et al., 2016). This – when applied to univariate MEG data – has been shown to effectively delineate bursts (Seedat et al., 2023b, 2020). Bursts are known to have a high beta amplitude, and with this in mind, the fact that bursts are less likely during periods of lower beta amplitude is hardly surprising. However, what is noteworthy is that a period of high beta could result from higher burst amplitude, increased duration, or a higher likelihood of bursts occurring (with the same amplitude and duration). Here our primary burst analyses (Figure 6.5) shows that it is possible to recreate the beta effect by only taking into account burst probability (which is independent of amplitude). Why this should be the case is unclear, though it is tempting to speculate that bursts are formed with a pre-specified amplitude (controlled by the number of synchronised cells in a network), and top down influence is mediated by modulating the number of these bursts. However, why bursting should provide an efficient means to inhibit cortical networks remains unknown and should be the topic of further study.

The current study has some limitations which should be mentioned. Firstly, to avoid confounds of a button press we had to eliminate from our final

analyses both the target probe stimuli, and stimuli where subjects incorrectly pressed a button. This meant in imbalance in attended and unattended probe stimuli and for our final analysis we had to remove (randomly) a selection of non-attended stimuli. This meant that a proportion of the data were lost in our analysis. A second limitation of the study design relates to the task timing. The beta response to somatosensory stimulation is traditionally characterised by a drop in beta amplitude during stimulation followed by a rebound (above baseline) on stimulus cessation (Pfurtscheller and Lopes da Silva, 1999). A good deal of evidence suggests that these two responses (at least following movement) have different neural generators – e.g. with localisations typically placing the rebound anterior in the brain compared to the beta decrease. It would be informative to know how attention modulates both the decrease and rebound independently, however here we only probed beta decrease relative to the resting blocks and the probe stimuli were presented so rapidly that the rebound was never allowed to evolve. Future studies should take this into account. Finally, here we used an HMM to identify bursting; this differs from the traditionally used methods which involve frequency filtering to the beta band, computation of the instantaneous beta envelope, and thresholding to find period of high amplitude. In principle the HMM provides a more principled approach, since the burst count, and burst durations are not defined by an arbitrary threshold applied to the envelope. Nevertheless, the HMM burst identification is affected by e.g. the mutual exclusivity and Markovian properties inherent to the model, and this should be considered when placing the present finding in the context of the current literature on bursts.

6.6 Conclusion

Using OPM-MEG we have successfully measured attentional modulation of beta oscillations in somatosensory cortex. We found significantly decreased beta amplitude during presentation of attended compared to non-attended stimuli. This is in agreement with previous findings from conventional-MEG and supports the notion that beta oscillations mediate top-down inhibition. Moreover, our analyses showed that attention has a similar effect on the occurrence of pan-spectral bursts; specifically, we measured significant reduction in the probability of burst occurrence, and the number of bursts per unit time, for attended compared to non-attended stimuli. In sum, our results provide evidence that attentional modulation of beta oscillations is driven by changes in pan-spectral burst occurrence and add weight to the argument that OPM-MEG could become the technique of choice for non-invasive electrophysiological measurements.

Chapter 7 Enabling ambulatory movement in wearable magnetoencephalography with matrix coil active magnetic shielding

7.1 Abstract

The ability to collect high-quality neuroimaging data during ambulatory participant movement would enable a wealth of neuroscientific paradigms. While the previous chapter demonstrated the sensitivity of OPM-MEG by measuring subtle attentional effects, this chapter aims to expand its broader capabilities. Harnessing the potential of OPM-MEG to allow participant movement could enable novel neuroscience experiments. However, as detailed in Chapter 3, the strict zero magnetic field requirement of OPMs means that systems must be operated inside a MSR and also require active shielding using electromagnetic coils to cancel residual fields and field changes (due to external sources and sensor movements) that would otherwise prevent accurate neuronal source reconstructions. In Chapter 5, we discussed how existing active shielding systems only compensate fields over small, fixed regions and do not allow ambulatory movement. Here we describe the matrix coil, a new type of active shielding system for OPM-MEG which is formed from 48 square unit coils arranged on two planes which can compensate magnetic fields in regions that can be flexibly placed between the planes. Through the integration of optical tracking with OPM data acquisition, field changes induced by participant movement are cancelled with low latency (25 ms). High-quality MEG source data were collected despite the presence of large (65 cm translations and 270° rotations) ambulatory participant movements. My contributions to this work include study conceptualisation, development and testing of methods to calibrate the multi-coil system, and data acquisition and processing for the phantom experiments. This was critical enabling work for the material in Chapter 8.

7.2 Introduction

Characterisation of the neural correlates of walking, gait and balance in conditions such as Parkinson's disease (Morris et al., 2001), stroke (Den Otter et al., 2005) and concussion (Guskiewicz et al., 2001) could be used to provide significant insight into diagnosis, stratification and prognosis. Indeed, access to non-invasive assessment of brain function during ambulatory movement would open up a wealth of interesting neuroscientific paradigms. Consistent with the arguments presented in Chapter 1, the available functional neuroimaging technology places significant limitations on experimental design and data quality. For example, fMRI requires participants to be enclosed in the scanner bore and remain motionless. Whilst EEG has excellent temporal resolution (~1 ms) and forms a wearable technology, enabling ambulatory movement studies

using treadmills ramps and stairs (Brantley et al., 2018; Wagner et al., 2019), it suffers from poor spatial resolution (~ 2 cm) (Baillet, 2017) and a high sensitivity to muscle artefacts during movement (Boto et al., 2019; Muthukumaraswamy, 2013). Functional near infrared spectroscopy (fNIRS) is similarly deployable, but (like fMRI) provides measurements of haemodynamic changes that are indirect reflections of brain function, and which have relatively poor spatial and temporal resolution. A robust, accurate, electrophysiological, measure of brain function during ambulatory movement would be a powerful platform for neuroscientific studies.

As seen in Chapter 3, OPM-MEG allows for the design of sensor arrays that can be adapted to the application of interest and crucially can move with the participant (Boto et al., 2018; Hill et al., 2020). It is the mobility of the sensor array that introduces the need for active shielding solutions. Recalling from Chapter 3, changes in sensor gain can adversely affect the quality of source modelling, both in terms of the fidelity of reconstructed time-courses of neural activity and the localisation of sources within the brain (Borna et al., 2022; Nugent et al., 2022). The saturation of the OPMs may be induced by drifts in the background field or the movement of the sensor array in a non-zero magnetic field (Hill et al., 2020, 2022; Holmes et al., 2019a; Iivanainen et al., 2019a). As detailed in Chapter 5, electromagnetic coils can be used to ‘actively’ shield equipment by generating a field which is equal and opposite to the field in the MSR.

Active shielding solutions have proven crucial for catalysing the development of OPM-MEG systems (Borna et al., 2020a; Holmes et al., 2018b, 2019b; Iivanainen et al., 2019b; Marhl et al., 2022; Rea et al., 2021b; Zhang et al., 2020). The bi-planar coil system described in Section 5.3.2 allowed seated participants to make small head movements during a scan, and enabled the acquisition of the first motion-tolerant MEG recordings with a wearable system (Boto et al., 2018). Additionally, precision modelling of the remnant field allowed the field to be further reduced to just 290 pT in a high performance MSR (Rea et al., 2021a). Other recent work has focused on improving the uniformity of field variations produced by coils operating inside magnetic shields by incorporating field distortions due to coils interacting with MuMetal (Kutschka et al., 2021; Packer et al., 2020; Zetter et al., 2020). However, although powerful, current active shielding technology does not allow measurement of brain activity during ambulatory movements.

Multi-coil systems utilise a series of individual ‘unit coils’ with a simple geometry, e.g. circular or rectangular windings (Borna et al., 2017; Juchem et al., 2011a; Packer et al., 2022). Coil currents are calculated based on knowledge of the magnetic field pattern generated by each coil in the system, such that the vector sum of the various fields form a magnetic field with a desired strength and spatial variation. Multi-coil systems can be considered to effectively ‘re-

design' themselves, offering flexibility in application. Such systems have been used successfully in magnetic resonance imaging to shim regions that experience local field variations (Juchem et al., 2011b, 2010) as well as in the operation, localisation, and calibration of OPM arrays (Borna et al., 2020b; Iivanainen et al., 2022) and in the development of lightweight MSRs for OPM-MEG with a large, fixed, volume of low remnant field (Holmes et al., 2022).

Here, a 'matrix coil' system is described, which is a reconfigurable multi-coil active shielding system comprising 48 square unit coils that continually recalibrates itself to compensate the magnetic field changes experienced by a sensor array that is freely moving. By combining an array of OPMs mounted in a 3D-printed helmet with optical tracking, the efficiency of each unit coil can be rapidly evaluated for the instantaneous sensor positions. Coil currents which best compensate the measured field changes experienced by the array are calculated and applied with low latency (25 ms). The matrix coil therefore potentially forms a basis for enabling ambulatory movement in OPM-MEG recordings. In this chapter, we first outline the mathematical framework used for matrix coil operation and describe the development of our system. We then detail four demonstrations of the system involving operation: (1) with a stationary array of OPMs; (2) as a seated participant makes small head movements; (3) in a phantom study to assess the effects on the system on source reconstruction accuracy and (4) during a MEG recording from an ambulatory participant.

7.3 Theory

The concepts involved in the calibration and subsequent nulling employed with the matrix coil system are equivalent to those covered in Section 5.3.2.3 of the magnetic shielding chapter. The field in the target volume can be described by the matrix equation

$$\Delta \mathbf{b}(t) = \mathbf{B}_{mat}(t) \boldsymbol{\beta}(t), \quad [7.1]$$

where the vector $\Delta \mathbf{b}(t)$ contains the change (relative to the measurement at time $t = 0$) in field measured by N sensors at time t , it is a column vector of N rows. Again, the design matrix $\mathbf{B}_{mat}(t)$ contains a model of the field or field gradient strength per unit of coefficient at each sensor. Therefore, obtaining a model of the background field requires solving equation 7.1, which can be done by evaluating

$$\boldsymbol{\beta} = \mathbf{B}_{mat}^\dagger \Delta \mathbf{b}. \quad [7.2]$$

In this case, the measured field $\Delta \mathbf{b}(t)$ can be fit to a low-order spherical harmonic model. The model is comprised of three uniform field components:

$$\begin{aligned} \beta_1 \hat{\mathbf{x}}, \{B_x\} \\ \beta_2 \hat{\mathbf{y}}, \{B_y\}, \\ \beta_3 \hat{\mathbf{z}}, \{B_z\} \end{aligned} \quad [7.3]$$

and five magnetic field gradient components:

$$\begin{aligned} \beta_4 (y\hat{\mathbf{x}} + x\hat{\mathbf{y}}), \left\{ \frac{dB_x}{dy} = \frac{dB_y}{dx} \right\} \\ \beta_5 (z\hat{\mathbf{x}} + x\hat{\mathbf{z}}), \left\{ \frac{dB_x}{dz} = \frac{dB_z}{dx} \right\} \\ \beta_6 (z\hat{\mathbf{y}} + y\hat{\mathbf{z}}), \left\{ \frac{dB_y}{dz} = \frac{dB_z}{dy} \right\} . \\ \beta_7 (-x\hat{\mathbf{x}} - y\hat{\mathbf{y}} + 2z\hat{\mathbf{z}}), \left\{ 2 \frac{dB_z}{dz} = -\frac{dB_x}{dx} - \frac{dB_y}{dy} \right\} \\ \beta_8 (x\hat{\mathbf{x}} - y\hat{\mathbf{y}}), \left\{ \frac{dB_x}{dx} = -\frac{dB_y}{dy} \right\} \end{aligned} \quad [7.4]$$

where the coefficient, β_n , describes the strength of the n^{th} component (see Rea et al., 2021a, and Mellor et al., 2022, for further details).

Now consider a series of M electromagnetic unit coils sited in the volume surrounding the sensors, each with an individual current i_m contained in the (M rows x 1 column) vector $\mathbf{i}$. If we define $\mathbf{F}$ as a (8 rows x M columns) matrix which describes the strength of each coefficient in the field model generated by a unit current applied to each coil (Rea et al., 2021a), then the total amplitude of each component generated by a set of coil currents is

$$\mathbf{F}\mathbf{i} = \boldsymbol{\beta}. \quad [7.5]$$

The coil currents required to cancel (negative sign) the model coefficients $\boldsymbol{\beta}$ found in equation 7.2 can be obtained by identifying the pseudo inverse matrix $\mathbf{F}^+$ and evaluating

$$\mathbf{i} = -\mathbf{F}^+ \boldsymbol{\beta}. \quad [7.6]$$

By combining Eq. 7.6, 7.1 and 7.2, the coil currents which best compensate the uniform field and field gradient components of $\Delta\mathbf{b}(t)$ are given as

$$\mathbf{i} = -\mathbf{F}^+ \mathbf{B}_{mat}^\dagger \Delta\mathbf{b}(t). \quad [7.7]$$

The quality of the solution (i.e. how well the produced field compares to the target field) will depend on the complexity of the target magnetic field pattern, the geometry of the matrix coil array, the size, shape, and number of unit coils in the array and the proximity of the OPMs to the edge of the volume enclosed by the coil set. The required coil currents may become physically unrealisable as field complexity increases; a constrained solver could be implemented to mitigate this issue, but the produced field pattern may then not be accurate enough for high-quality shielding.

7.4 Methods

7.4.1 Coil design

We used a system of 48, 38.5-cm square, coils mounted on two 1.6 x 1.6 m² planes separated by 1.7 m as shown in Figure 7.1a. Each plane contained 24 coils arranged as a 4 x 4 grid that filled each plane, along with an overlapping 3 x 3 grid (excluding the central coil) offset by half the grid spacing. The overlapping grid helps to provide regions of opposing current flow that are required to generate magnetic fields along all three Cartesian axes, despite the coil windings being constrained to a single plane. This design mimics the bi-planar coils described in previous works (Holmes et al., 2019a, 2018a), allowing the generation of coil current distributions which approximate the distributed windings as shown in Figure 7.1c-d. The system was constructed using two wooden boards, a photograph of one plane of the completed system is shown in Figure 7.1b. Plastic plates with wire guides were attached to the corners where each coil was to be mounted to aid winding. Each unit coil was wound by hand, using 10 turns of 0.56 mm diameter enamelled copper wire (unit coil resistance ~2 Ω, unit coil inductance ~160 μH, coil mutual inductance is maximum between adjacent elements and is <10 μH). Each unit coil was connected to a series of terminal blocks at the base of the large boards by twisted pair windings. When positioned inside the MSR, the terminal blocks were connected to a series of multi-core cables which exited the MSR to be connected to the driving electronics.

7.4.2 Driving electronics

The low-noise coil drivers were constructed in house. The drivers consisted of 12, 4-channel, amplifier boards each operated in voltage feedback mode. Each amplifier channel uses LM324A op-amps (Texas Instruments, Texas, USA) with a $220\ \Omega$ resistor added in series to limit current outputs to ± 45 mA per channel from ± 10 V input voltage (the series resistor reduces magnetic field fluctuations induced by voltage noise from the DACs). Voltage inputs to the drivers were provided by three National Instruments (NI, Texas, USA) NI-9264 16-bit, ± 10 V, 16-channel, digital to analogue converter (DAC) cards mounted in a NI-cDAQ-9174 data acquisition (DAQ) chassis interfaced with the NI-DAQmx package in MATLAB (MathWorks Inc., Natick, MA, USA).

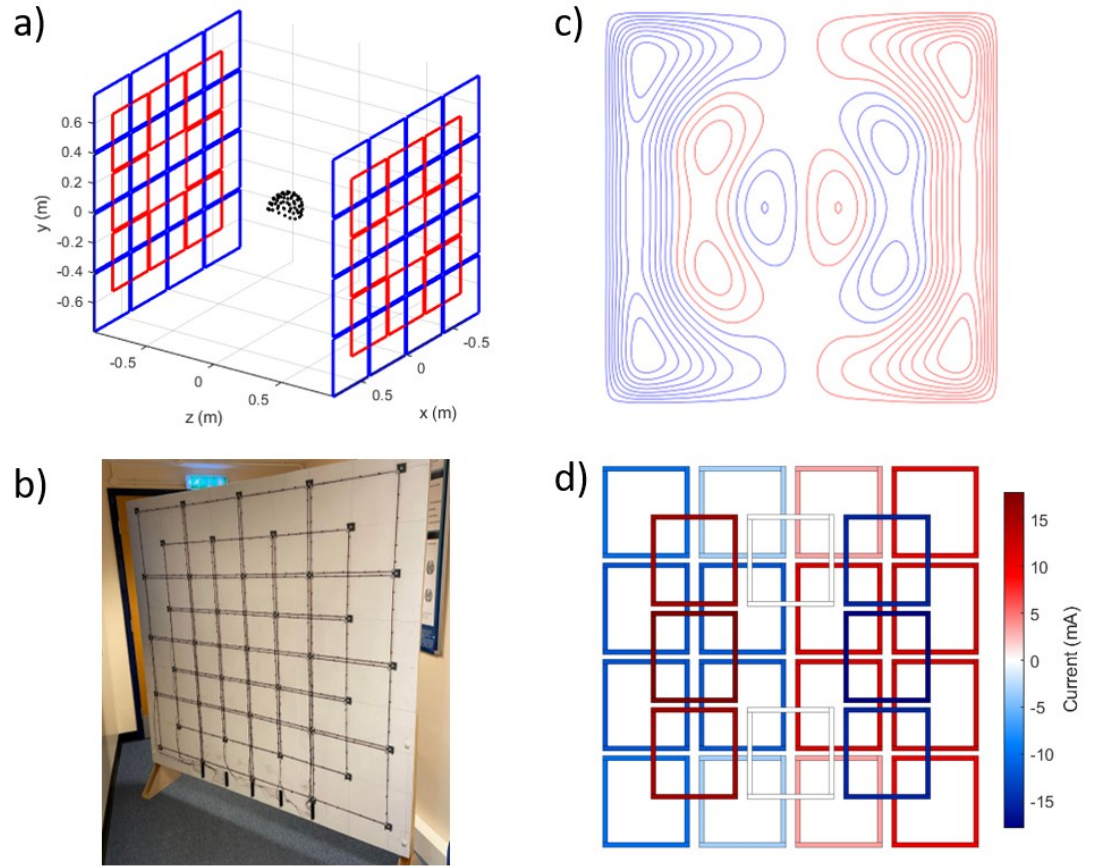


Figure 7.1: The matrix coil active magnetic shielding system. (a) System is arranged in a bi-planar geometry and each plane contains 24 square coils arranged in an overlapping grid pattern. The blue and red colours highlight the 4×4 grid of coils and the overlapping 3×3 (excluding the central coil) set of coils. The black dots represent the positions of OPM sensors in a 3D printed helmet placed at the centre of the coils. (b) Photograph of a single plane of the constructed coil system. (c) the distributed windings of one plane of a bi-planar coil designed to generate a uniform magnetic field in the x-direction (see (a)) over a $40 \times 40 \times 40 \text{ cm}^3$ volume at the centre of the two planes with deviation $< 5\%$ from the target magnetic field. Such designs have been used in previous OPM-MEG experiments. Red and blue denote regions of opposing current flow. The second plane (not shown) features the same windings, but the current directions are reversed with respect to the first plane. (d) The currents applied to one plane of the matrix coil to generate the same field as the coil shown in (c), note the similarity between the two designs in terms of current distribution and direction of current flow. The current directions in the second plane are again reversed.

7.4.3 OPMs and helmet

We employed the same system as the one described in the previous chapter. Again, this includes an array of QuSpin's zero field OPMs (3rd generation, triaxial variant). The array was housed in a MSR with 4 layers of MuMetal and 1 layer of copper with internal dimensions of $3 \times 2.4 \times 3 \text{ m}^3$

(MuRoom, Magnetic Shields Limited, Kent, UK) which was demagnetised prior to the start of each experiment leaving a remnant field of ~ 2 nT at the centre of the room. The sensors then measure changes in magnetic field relative to an initial zero field point. The field zeroing and calibration of the array was performed using the manufacturer's software (QuSpin ZFM UI V9). The analogue output of each sensor was connected to a series of NI-9205, 16-bit, 32-channel, analogue to digital converter (ADC) cards mounted in a NI-cDAQ-9179 DAQ chassis. Each channel was sampled at 1,200 Hz using the NI-DAQmx package in MATLAB. The sensors were mounted in a rigid, 3D-printed helmet (Cerca Magnetix Limited, Nottingham, UK) such that the position and orientation of each of the three measurement axes of each sensor, were known in the coordinate frame of the helmet model (Hill et al., 2020).

7.4.4 Optical tracking

To calibrate the system via simulation of unit coil fields, we need to know the position and orientation of the OPMs in the helmet with respect to the unit coils. We again used an optical tracking system (OptiTrack, Flex13, NaturalPoint Inc., Oregon, USA) which uses a series of six cameras mounted around the MSR to track the position of a series of infrared reflective markers. Such cameras have been used in previous OPM-MEG studies. Aside from a sharp interference peak at the frame rate of the camera (120 Hz) they do not otherwise interfere with the OPM data (Holmes et al., 2018a; Roberts et al., 2019; Seymour et al., 2022, 2021). A rigid body of three or more markers (which do not move with respect to each other) can be formed to provide 6-degree-of-freedom (pitch (nodding the head), yaw (shaking the head) and roll (tilting the head) rotations and translations) tracking of the centre of mass of the markers. Here we used a fixed marker set of 5 markers on one coil plane to act as a static reference. A second rigid body was formed by placing 5 markers at known positions on the helmet. We used the NatNet SDK 4.0 software package to interface Motive (the optical tracking camera software, NaturalPoint Inc.) with MATLAB. Specifically, data are streamed from Motive such that MATLAB can poll motion capture data at any time in order to obtain the position of the two rigid bodies within a single frame of the camera. By prior measurement of the coil plane positions with respect to the MSR we applied a coordinate transform to place the helmet and coil rigid bodies into the MSR frame of reference (Rea et al., 2021a).

7.4.5 Implementing the nulling

The nulling process was implemented in MATLAB. Firstly, the known position of each sensor with respect to the coil set was obtained by polling the optical tracking data stream and computing the coordinate transform. We then used the Biot-Savart law to calculate the magnetic field generated by a unit current in each unit coil at each sensor. These changes are decomposed into the

uniform field and field gradient spherical harmonics (using the centre of mass of the OPM-MEG helmet as the origin of the model) (Mellor et al., 2022; Rea et al., 2021a) and are used to form the matrix $\mathbf{F}$ (and its corresponding pseudo-inverse matrix $\mathbf{F}^+$). We then use the helmet positions to form the matrix $\mathbf{B}_{mat}$ (and its corresponding pseudo-inverse matrix $\mathbf{B}_{mat}^+$) and calculated $\Delta\mathbf{b}$ as the difference between the mean of the most recent 30 samples of incoming data (30 samples collected at 1,200 Hz sample rate is equivalent to 25 ms of data, an effective data rate of 40 Hz) from each channel and the mean of the first 30 samples of the recording such that the matrix coil is only compensating the change in field experienced by the array relative to its starting field, rather than the absolute remnant field over the helmet. By using the measured resistance (R) of each coil circuit and equation 7.7, the required nulling voltages can be calculated as

$$\mathbf{V} = R\mathbf{i} = -R\mathbf{F}^+\mathbf{B}_{mat}^+\Delta\mathbf{b}. \quad [7.8]$$

As the process is continuous, and will be sensitive to noise in the data and inaccuracies in the modelling, the voltage at timepoint k is updated with a gain K_p (<1) such that

$$\mathbf{V}_{k+1} = \mathbf{V}_k - K_p R\mathbf{F}^+\mathbf{A}^+\Delta\mathbf{b}. \quad [7.9]$$

A limit is placed such that if any value of $\mathbf{V}$ exceeds the 10 V range of the DAC it is limited to 10 V. The nulling voltage updates at a rate of 40 Hz, the program stores helmet position information and applied coil currents at the same rate. The rate limiting step is the time taken to calculate the field from the unit coils. Vectorisation and pre-calculation of other information was used to focus on this step during nulling. The value of K_p was empirically chosen as 0.4. If K_p is too large the system will become unstable resulting in a large low-frequency oscillation in the OPM data. This behaviour is common in poorly tuned feedback controllers. If K_p is too small, then minimal shielding occurs. Figure 7.2a shows a schematic overview of the system, and Figure 7.2b shows a flowchart of the nulling process.

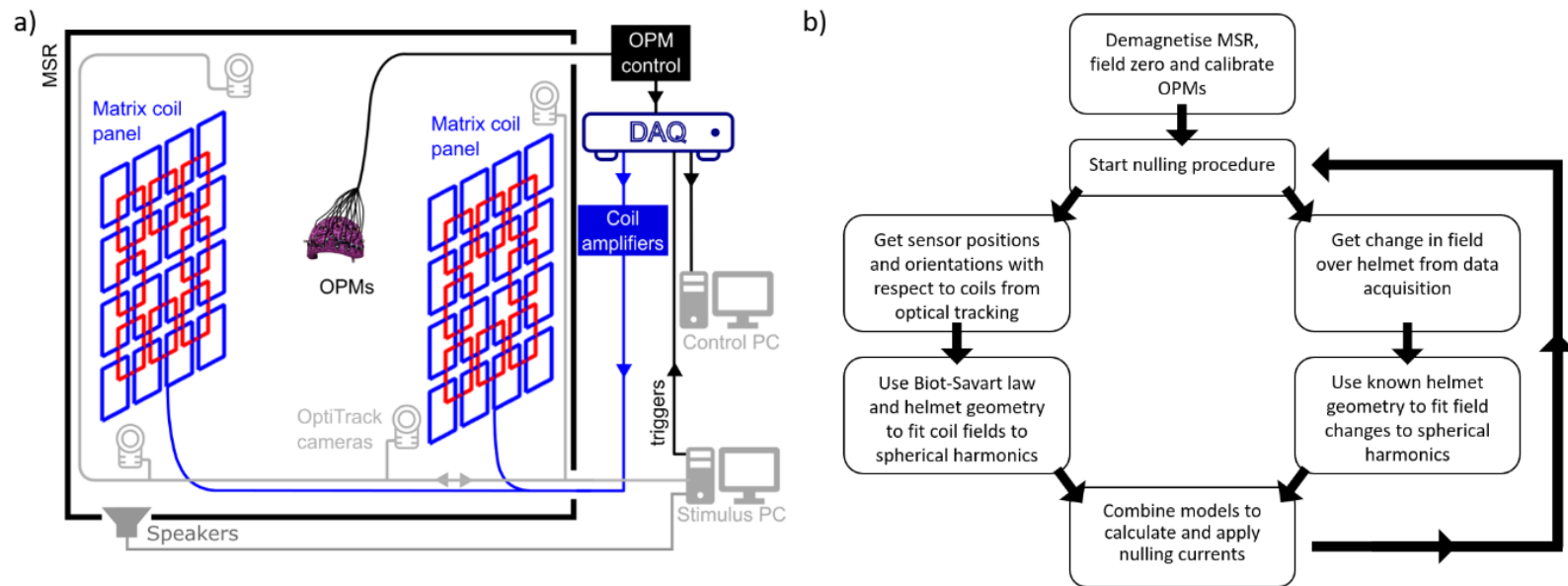


Figure 7.2: System schematic and nulling procedure flowchart. *a)* Overview of OPM-MEG system with matrix coils. The system is housed in a magnetically shielded room. Coil panels are placed either side of a participant wearing a helmet that contains OPMs. A control PC is used to read incoming data from the OPMs and optical tracking cameras then combine these data to calculate and apply nulling currents. A separate PC is used during MEG experiments to provide (in this case) auditory stimulation to a participant via a set of speakers. Trigger channels are used to synchronise the stimuli to the OPM recording. *b)* Flowchart of continuous field nulling process.

7.5 Results

7.5.1 Compensating field drifts measured by a stationary array

We placed 14 triaxial OPMs into the rigid helmet, giving 42 measurement channels. Sensor positions were evenly distributed to characterise the field and field gradient over the helmet. The helmet was deliberately placed away from the centre of the matrix coil, as shown in Figure 7.3a, to demonstrate the system's flexibility. For all experiments, the MSR was demagnetised, and the OPMs were zeroed and calibrated prior to recording. Data were collected for 600 s. For the first 300 s the matrix coil system was not active (0 mA applied to each unit coil) and for the final 300 s the matrix coil was activated to cancel the changes in field and field gradient over the helmet.

Figure 7.3b shows the change in field measured by the OPMs during the experiment. The absolute maximum change in field is reduced from 310 pT to 14 pT, a shielding factor of 13.7. Figure 7.3c shows the currents applied to the unit coils throughout the experiment. Nulling is achieved with an absolute maximum current value of 0.37 mA. Note the similarity of the variation of the applied coil currents in the second half of the recording with the field variation manifested in the first half of the recording. Figure 7.3d shows the median value of the power spectral density of the data across all sensors for each half of the experiment separately. Significant reduction in the low frequency (0.1 – 1 Hz) fluctuations is achieved with the noise level rising at higher frequency. The broadband interference is a consequence of the changes in magnetic field induced by the matrix coils over the helmet. The strength of this interference is determined by the strength and the rate of change of the artefacts being compensated (as the matrix coil field changes will increase accordingly), and the bit-depth of the DACs (the smallest field variation that can be accurately corrected is set by the field amplitude corresponding to the least-significant bit; this should ideally be smaller than the OPM noise level, but this is not the case here due to the use of 16-bit DACs and the coil drivers' large dynamic range, which is needed to compensate a wide range of magnetic field strengths during participant movements).

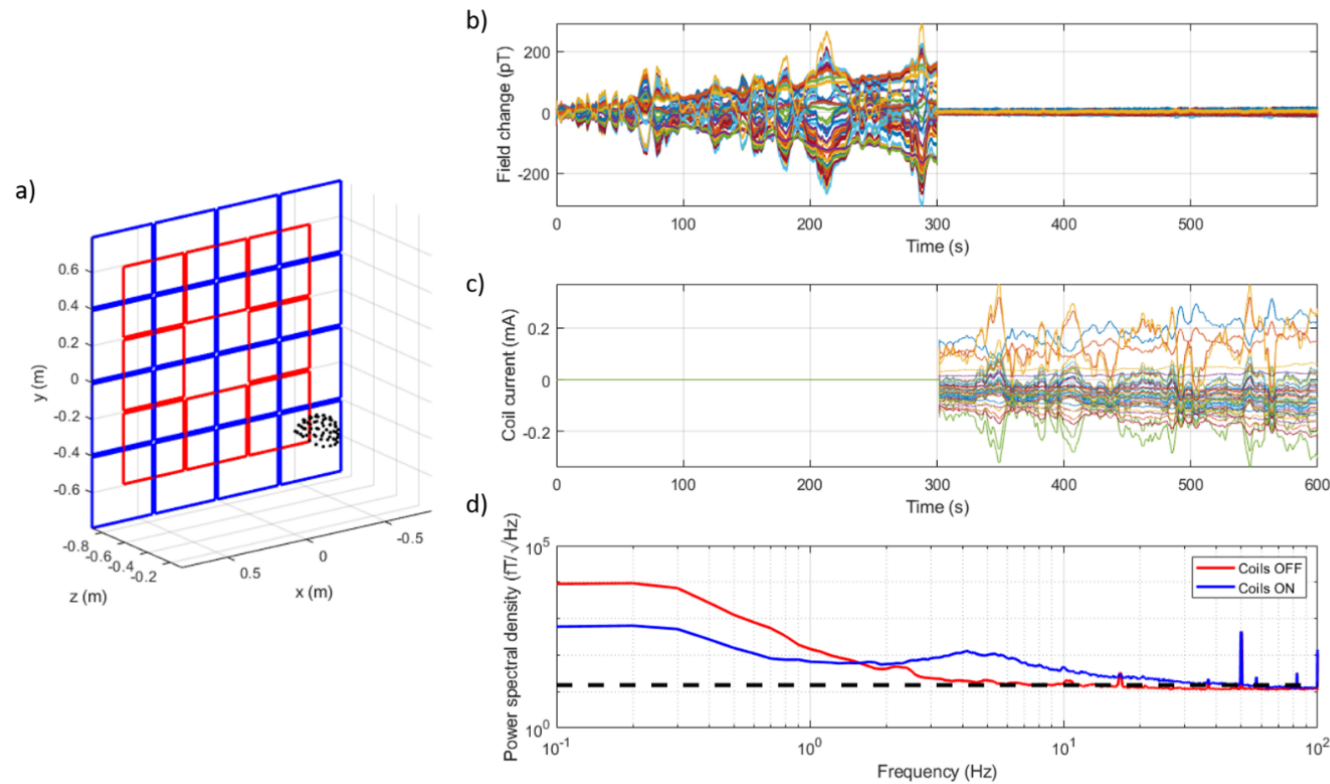


Figure 7.3: Compensating magnetic field drifts on a fixed array of OPMs. *a)* The position of the helmet containing 15 triaxial OPMs with respect to one plane of the matrix coils. The helmet is deliberately positioned off centre in the x, y and z directions to showcase the flexibility of the matrix coil system to generate the required compensation fields at multiple locations between the planes (helmet centre of mass $(x,y,z) = (0.15, -0.24, 0.18)$ m). *b)* Magnetic field drifts recorded by the OPMs over a period of 600 s. Each colour represent an individual channel. For the first 300 s the matrix coil system was not active, for the final 300 s the matrix coil compensated changes in the uniform field and field gradients over the helmet. *c)* The current applied to each of the 48 coils throughout the experiment. Each colour represents an individual coil current. Note the similarity between the profile of the field changes in the first half of the experiment and the current variations in the second half of the experiment. *d)* The power spectral density of the data measured by the OPMs with the coils off (red) and with the coils on (blue). The low-frequency noise level is reduced by the matrix coil, but an increase in noise is seen at higher frequencies. The black dashed line indicates 15 fT/√Hz, the noise floor of the OPMs used in the experiments.

7.5.2 Compensating artefacts on a moving array

The same helmet was then worn by a participant (male, 28, right-handed). The participant was instructed to complete a series of rotations and translations of their head about each axis in turn while seated at the centre of the matrix coil system. Data were recorded for 120 s; for the first 60 s the matrix coil was not active and for the final 60 s the matrix coil was used to compensate changes in the field and field gradient over the helmet. Rotation and translation with respect to each axis was performed twice in each half of the experiment.

Figure 7.4a shows the change in field measured by the 15 OPMs during the experiment. The absolute maximum change in field is increased compared to the static case (Figure 7.3b) due to helmet movement and was reduced from 952 pT to 185 pT by the matrix coil system, a shielding factor of 5.2. Figure 7.4b shows the currents applied to the unit coils throughout the experiment. Nulling is achieved with an absolute maximum current value of 1.05 mA. Again, note how the variation in the measured fields due to helmet movement is mimicked by the applied coil currents. Figure 7.4c shows the change in position of the centre of mass of the helmet during the experiment. Figure 7.4d shows the change in rotation of the centre of mass of the helmet during the experiment. Table 7.1 shows the range of translation and rotation during the experiment. Helmet movements were consistent in the two halves of the experiment, but the measured motion artefact was reduced when the matrix coils were on. Figure 7.4e shows separate plots of the median value of the power spectral density across all sensors for each half of the experiment. We note the increase in noise level for both recordings compared to the results shown in Figure 7.3 due to the brain noise from the volunteer. Again, the coil system reduces the noise level for low frequency field variations, but the noise is increased at higher frequencies. As the field changes induced in this experiment are stronger, and have a higher rate of change of field, than in the fixed helmet case, the matrix coil generates higher amplitude interference in the measured data, producing a broad ‘bump’ in the noise spectra at 40 Hz, with a harmonic at 80 Hz. The 40 Hz bump appears as the magnetic field produced by the matrix coils is being updated at this rate. This results in discontinuous ‘steps’ of magnetic field in the magnetometer time-course data. These steps have a varying amplitude, but an effective frequency of 40 Hz. As the steps are irregular and not sinusoidal, a broadened peak centred at 40 Hz is produced in the PSD (with a corresponding harmonic at 80 Hz).

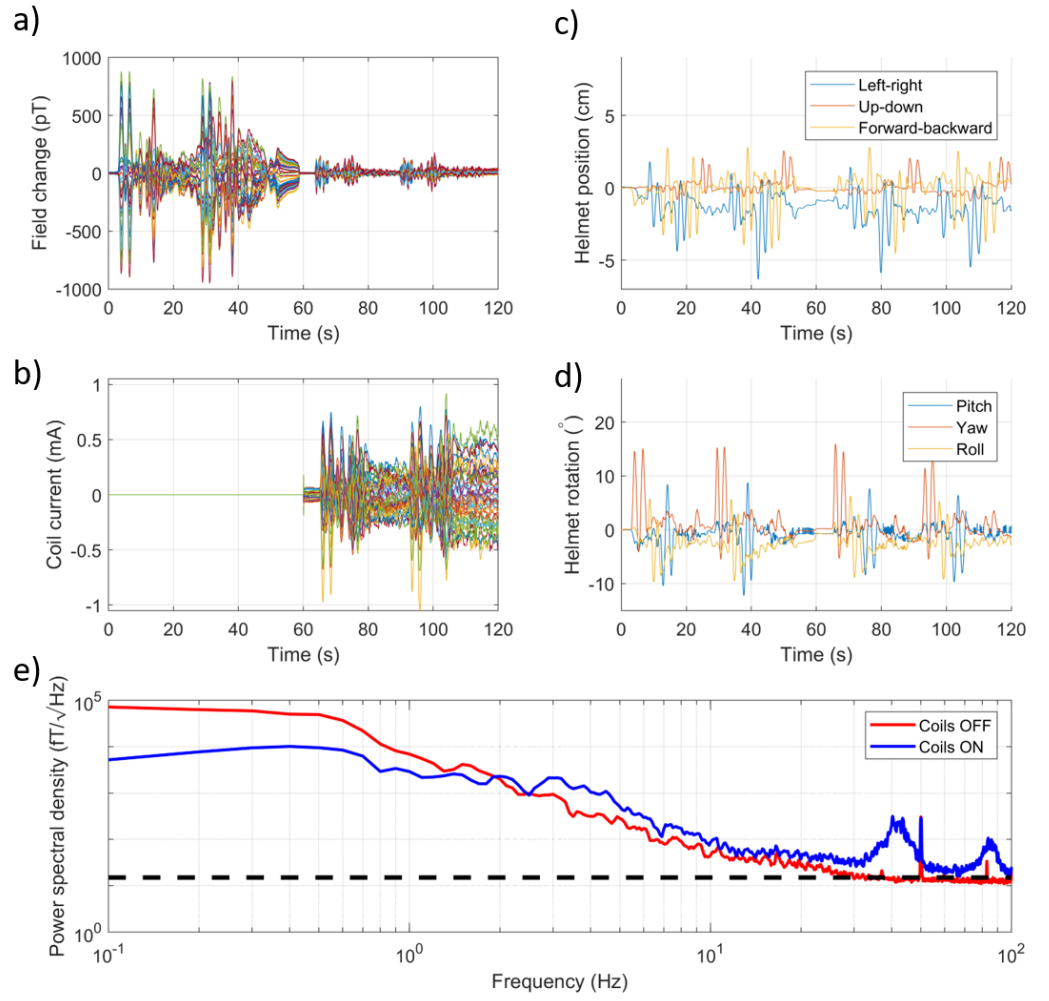


Figure 7.4: Compensating magnetic field changes on a moving array of OPMs. *a)* Magnetic field changes recorded by the OPMs over a period of 120 s whilst a seated volunteer made controlled head movements. For the first 60 s the matrix coil system was not active, for the final 60 s the matrix coil compensated changes in the uniform field and field gradients over the helmet. *b)* The current applied to each of the 48 coils throughout the experiment. *c)* The change in the position of centre of mass of the helmet during the experiment. *d)* The rotation of the helmet about the centre of mass during the experiment. Note the size of the movement remains similar throughout the recording, but the amplitude of the artefact is significantly reduced by the matrix coil in the second half of the recording. *e)* The power spectral density of the data measured by the OPMs with the coils on (blue) and with the coils off (red). Compensating a stronger and more quickly varying field results in a large artefact at 40 Hz (the rate at which coil currents are updated). The black dashed line indicates 15 fT/√Hz.

	Translations (cm)			Rotations (°)		
	Left-right	Forward-backward	Up-down	Pitch	Yaw	Roll
<i>Seated head movement</i>						
Matrix coil ON	8.1	7.0	3.4	21.0	20.9	15.4
Matrix coil OFF	7.3	7.3	3.1	17.3	21.4	15.5
<i>Ambulatory MEG task</i>						
Matrix coil ON	57.0	50.5	62.7	215.1	173.4	270.3
Matrix coil OFF	56.7	49.9	64.6	63.00	164.9	108.5

Table 7.1: The range of **translation and rotation** of the OPM-MEG helmet during the moving array experiments.

7.5.3 Preventing motion-induced sensor gain changes: phantom study

To investigate the capability of our system to collect high-quality MEG data despite significant participant motion, and the presence of broadband artefacts induced by the matrix coil system, we conducted a phantom study. A dry-type current dipole phantom was constructed according to the design used by Oyama et al. (Oyama et al., 2015). Here, the dry current dipole phantom is an electromagnetic coil with the wirepath forming an isosceles triangle, with 5 mm base and 45 mm height. A 3D-printed plastic former was constructed with slits to guide the winding of a single turn of 0.56 mm diameter enamelled copper wire as shown in Figure 5a. The remaining wire was twisted together to avoid production of stray magnetic fields. To ensure the dipole phantom remained fixed in position with respect to the OPMs in the helmet during movement a Perspex cylinder was connected to an empty OPM casing into which the phantom was glued, the casing could then be fixed into any slot in the OPM-MEG helmet. The base of the current path was positioned 30 mm beneath the inner surface of the OPM helmet and was oriented tangentially to the helmet surface to mimic a neuronal source. The dipole phantom was inserted into a centrally positioned slot within the helmet as shown in Figure 7.5b.

We conducted a simple experiment to measure the effects of motion through a non-zero background field on OPM data. The OPM-MEG helmet containing the phantom and 23 triaxial OPMs (69 total channels, with sensor positions and orientations shown in Figure 5c relative to the surface of the brain of the template head which was used to design the helmet (see (Hill et al., 2020) for details on how the generic OPM-MEG helmets are designed)) was positioned at the centre of the matrix coil system. The helmet was initially positioned as if a participant was facing forward (Position 1). The MSR was demagnetised and a small (~5 nT) magnetic field oriented in the z-direction was applied using a (distributed winding) bi-planar coil (Holmes et al., 2019). The

OPMs were field zeroed and calibrated in this B_z field at Position 1 prior to the start of the experiment. A 23 Hz sinusoidal current was then passed through the phantom (amplitude 200 nA, producing a maximum measured field of 20 pT). This current was applied for 4.2 seconds, followed by a 2 second ‘rest’ period during which no current was applied to the phantom. The waveforms were generated by MATLAB interfaced with a NI-9264 DAC at a sample rate of 10 kHz, and a trigger signal was used to synchronise the OPM data with the timings of the current waveform applied to the phantom. An audio cue (also generated by MATLAB) then instructed an experimenter inside the MSR to rotate the helmet (as if shaking the head to the right) by approximately 25° (Position 2). After 5 seconds had passed the experiment was repeated, and an audio cue instructed the experimenter to rotate the helmet a further 25° (Position 3, $\sim 50^\circ$ rotation from Position 1). The process was repeated 60 times cycling through each position in the order: 1, 2, 3, 3, 2, 1, 1, 2, 3, 3, etc. such that 20 trials were collected in each position. The experiment was repeated with and without the matrix coils active. For the experiment without the matrix coils, the OPMs were operated in a mode where the operational range is increased from ± 1.5 nT to ± 5 nT (0.33x gain mode button on QuSpin UI, dynamic range is increased at the expense of bit-precision and effects of sensor gain changes). The increased dynamic range was needed to accommodate the larger field changes without signal clipping. We also conducted two further experiments where all 60 trials were collected whilst the helmet remained fixed in position 1 with, and without, the matrix coils active. We hypothesised that with the matrix coils inactive, movement in the 5nT B_z -field would produce changes in the measured amplitude of the phantom signal, due to sensor gain changes resulting from variation in the ambient field experienced by the sensors. In contrast, with the matrix coils active, the amplitude of the signal from the phantom was expected to be relatively unaffected by movements. We further hypothesised that these gain changes would affect the accuracy of source reconstructions due to discrepancies between the measured data and the MEG forward model (Borna et al., 2022; Nugent et al., 2022).

7.5.4 Effects of sensor gain changes

From the known timings of the experiment, we first segmented data into trials (each trial was 6.2 s, 0 s - 4.2 s was the sinusoidal waveform with the final 2 s as the rest period) using the trigger signals. For each trial, from each of the four experiments, we then extracted the magnetic field measured by each of the 69 OPM channels during the final 2 seconds of the 4.2 second ‘stimulation’ period (to isolate a period where the helmet was relatively still to ensure the FFT amplitude was not affected by movement artefacts). For each chunk of data, we calculated the mean value (which we refer to as the field offset, the change in field relative to the initial field zero point of the sensor) and extracted the amplitude of the 23 Hz peak by computing the fast Fourier transform. Figure 7.5d and 5e show the amplitude of the phantom signal as a function of the field offset for the channel (highlighted in green in Figure 5c) with the largest absolute field offset value in the experiment when the helmet was moving without the

matrix coils active. This reflects the worst-case scenario, in fact the total absolute maximum field offsets across all channels were between 325 and 3,620 pT, with the values dependent on the orientation of the channel's sensitive axis with respect to the axis of rotation (~about the vertical y axis) and the applied magnetic field (B_z , meaning channels with an ~y orientation will see little effect whilst sensors with ~x-z orientations will experience larger field changes). Table 7.2 summarises the range of motion parameters of the helmet, along with the field offset values and phantom signal amplitudes for the channel shown in Figure 7.5c, for all four experiments. We note that despite similarly sized rotations and translations in both movement experiments, in the case where the helmet moves without the matrix coils active the mean and standard deviation of the amplitude of the phantom signal for positions 1, 2 and 3 respectively were 11.9 ± 0.1 pT, 10.4 ± 0.2 pT and 8.9 ± 0.2 pT compared to 11.8 ± 0.1 pT, 11.8 ± 0.1 pT and 11.6 ± 0.1 pT for the experiment repeated with the matrix coils active. The range of field offset values across all positions was decreased from 3,605 pT to 39 pT using the matrix coils. The variation in both the mean value and the range of phantom signal strengths are due to sensor gain changes as the background field experienced by the OPM moves away from zero, consequently the true field offset values are likely to be larger than reported. The experiment shows that the matrix coil can compensate the motion-related field changes which induce these gain changes, ensuring the phantom signal is accurately measured.

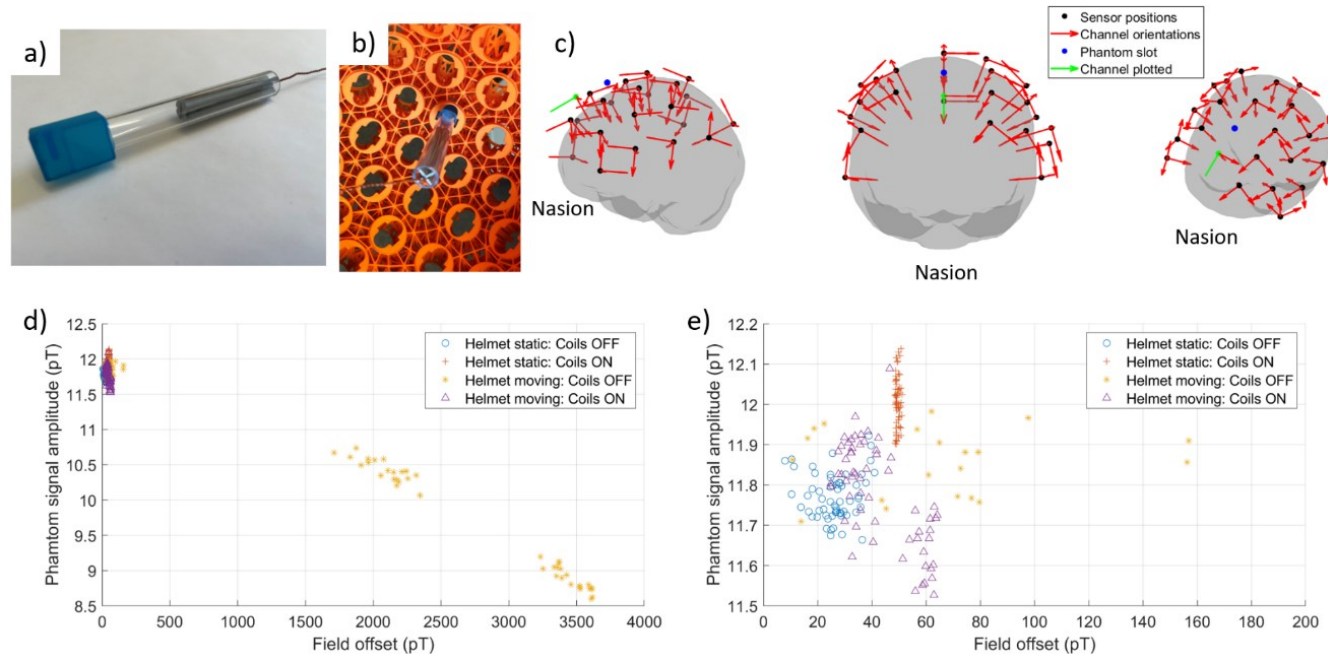


Figure 7.5: Dry current dipole phantom and sensor gain experiments. *a)* Photograph of the dry-type current dipole phantom used in these experiments. The phantom coil is an isosceles triangle wound around a (grey) plastic former with base 5 mm and height 65 mm. An empty (blue) OPM casing is attached to a (clear) Perspex cylinder into which the phantom coil is glued. *b)* Photograph of the phantom inside the OPM-MEG helmet. The empty OPM casing can be inserted into any slot in the helmet, the base of the coil is 30 mm beneath the inner surface of the helmet. *c)* Each of the 23 triaxial OPMs (black dots) used in the experiment are shown around the template brain, which was used to design the helmet surface. Red arrows indicate the three channel orientations for each OPM. The slot into which the phantom was inserted is shown in blue. *d)* Plot of the field amplitude measured on a single channel (indicated by the green dot and arrow in *c)*) due to a 200 nA, 23 Hz phantom signal. Results are shown for four experimental cases. Note that during the experiment in which the helmet moved but the matrix coils were not active a large range of field offsets and phantom signal amplitudes are recorded due to sensor gain changes as the field experienced by the OPM moves away from zero. *e)* Zoomed in plot of data for low field offsets (0 - 200 pT) to show consistency of measured source amplitude in the other three experiments.

Condition	Translations (cm)	Rotations (°)	Helmet Position	Phantom signal amplitude (pT)	Field offsets (pT)
Static: Coils OFF	n/a	n/a	1	11.8 ± 0.1	26 ± 8
Static: Coils ON	n/a	n/a	1	12.0 ± 0.1	50 ± 1
Moving: Coils OFF	Left-right: 3.4 Up-down: 0.3 Forward-backward: 10.1	Pitch: 5.9 Yaw: 54.0 Roll: 7.4	1	11.9 ± 0.1	64 ± 41
			2	10.4 ± 0.2	2,086 ± 170
			3	8.9 ± 0.2	3,456 ± 126
Moving: Coils ON	Left-right: 4.6 Up-down: 0.4 Forward-backward: 8.9	Pitch: 5.2 Yaw: 44.1 Roll: 6.0	1	11.8 ± 0.1	31 ± 3
			2	11.8 ± 0.1	39 ± 5
			3	11.6 ± 0.1	60 ± 3

Table 7.2: The range of **translation and rotation** of the OPM-MEG helmet and the measured amplitude of the phantom signal, and level of field offset (both mean ± standard deviation) for the OPM sensor showing the largest field change recorded during the phantom experiments.

7.5.5 Effects on source reconstruction

To investigate the effect of the matrix coils and sensor gain changes on reconstruction of the phantom source we separately employed a linearly constrained minimum variance beamformer (Vrba and Robinson, 2001) and a single equivalent current dipole fitting analysis (Hämäläinen et al., 1993).

7.5.5.1 Beamformer analysis

Source-space projection of the sensor signals was carried out using a linearly constrained minimum variance (LCMV) beamformer. As described in Section 4.8, this spatial filtering technique estimates a current dipole timecourse $\hat{\mathbf{q}}_{\theta}(t)$ using a weighted sum of the measured data $m_i(t)$:

$$\hat{\mathbf{q}}_{\theta}(t) = \sum_{i=1}^N w_{i,\theta} m_i(t), \quad [7.10]$$

where $w_{i,\theta}$ are the beamformer weights and N is the number of magnetometer channels. Solving for the weights using a Lagrange multiplier yields the matrix equation:

$$\mathbf{w}_\theta^T = \frac{\mathbf{l}_\theta^T \mathbf{C}^{-1}}{\mathbf{l}_\theta^T \mathbf{C}^{-1} \mathbf{l}_\theta}, \quad [7.11]$$

where $\mathbf{C}$ is the sensor data covariance matrix and $\mathbf{l}_\theta^T$ is the forward field vector containing the solutions to the forward problem for a unit dipole at θ .

Prior to beamformer analysis we applied homogeneous field correction (Tierney et al., 2021) to the OPM data to remove spatial patterns of field variation over the array that result from uniform magnetic field components (and as such are unlikely to reflect neuronal activity). Homogeneous field correction was also applied to the forward field vectors. Arrays of triaxial OPMs have been shown to have excellent interference rejection properties due to their ability to better distinguish between neuronal sources and external interference (Boto et al., 2022; Brookes et al., 2021; Tierney et al., 2022). We expected the combination of the beamformer, homogeneous field correction and triaxial sensitivity would allow us to recover the underlying MEG signal whilst simultaneously compensating the nulling artefacts.

The source space used here was a regular grid of 4 mm, cubic voxels which span the ‘brain’ of the template head that was used to design the helmet. The forward field vectors were calculated using a single-sphere model and the current dipole approximation (Sarvas, 1987). 1% regularisation was applied to the covariance matrices. The source orientation was determined by generalised eigenvalue decomposition as described by Sekihara et al., 2004. This method differs from the scalar beamformer approach described in Section 4.8 in that it is a vector beamformer, which yields three-dimensional source orientation information rather than just source magnitude. Analysis was performed in MATLAB using bespoke software written in house.

We first filtered the OPM dataset between 13 and 30 Hz (using fourth order, Butterworth filtering). Activation maps were then generated using a pseudo-T-statistic, as detailed in Section 4.10.2. First, two covariance matrices for the active and control periods, $\mathbf{C}_a$ and $\mathbf{C}_c$ respectively were constructed, and a pseudo-T-statistical contrast map was calculated for each source location as

$$\mathbb{T} = \frac{Q_a - Q_c}{2Q_c}, \quad [7.12]$$

where $Q_a = \mathbf{w}^T \mathbf{C}_a \mathbf{w}$ and $Q_c = \mathbf{w}^T \mathbf{C}_c \mathbf{w}$. Pseudo-T-statistics were computed at the vertices of the 4 mm grid spanning the entire source space. The active window was chosen to be 2.5 to 3 seconds following the signal onset and the

control window was chosen to be 4.5 to 5 seconds. The location of the peak activation and corresponding estimated source orientation were then extracted from each activation map.

7.5.5.2 Dipole fitting analysis

Although the noise rejection properties of the beamformer are likely to be of significant benefit for source reconstructions on low SNR data in the presence of large artefacts, we also implemented a dipole fit to further investigate differences in the source reconstructions due to changes in sensor gain. Specifically, we estimated the position and orientation of a single current dipole with unit (1 nAm) dipole moment that produces the maximum correlation between the lead fields of the simulated source and the measured data. The dipole fitting was implemented using MATLABs constrained minimisation function *fmincon*, with constraints on the dipole position such that it could only exist within the source space. For a given source position, the source orientation was estimated by assuming the dipole to be oriented tangentially to the template brain surface and computing a lead field ‘sweep’ for all possible dipole orientations in this tangential plane (between 0 and 180°, in steps of 1°). We then identified the orientation with the highest correlation between the lead field and the measured data and used this value in our objective function. Once the best fitting dipole was found, the dipole moment was estimated via linear regression of the lead field pattern produced by the estimated dipole with the measured data.

7.5.5.3 Quantifying changes

For both analyses, we first found the source location and orientation for the experiment in which the helmet did not move, and the matrix coils were not active. These serve as our ‘ground truth’ measurements (note we did not use the measured position of our source in the helmet to compare to as we wished to focus on the difference between datasets) to which all subsequent data are compared. The ground truth data were comparable for beamformer and dipole fitting, source positions: voxel position [3.50,19.5,42.5] mm for the beamformer and position [3.32,21.5,42.4] mm for the dipole fit, with source orientations: [0.26,0.58,-0.77] for the beamformer and [0.25,0.56,-0.79] for the dipole fit, the estimated dipole moment was 1,324 nAm. Table 7.3 summarises the Euclidean distance between the peak location (peak voxel location for beamformer analysis) and the ground truth values, the angle between the orientation vectors and the ground truth values and the estimated dipole moments for all conditions and experiments. The results show that for the experiment in which the helmet remained still, but the matrix coil was active, the beamformer was able to localise the phantom to the same 4 mm voxel as found in the ground truth measurement, with a change in orientation of just 0.05°, compared to a change of 0.067 mm and 0.046° and no change in dipole moment for the dipole fit. For the moving phantom experiment during which the matrix coil was active, the source was

again localised to the same voxel as the ground truth for all positions with a change in orientation of $0.29^\circ/0.93^\circ/1.50^\circ$ for Positions 1/2/3 respectively, compared to a change of $0.16/0.27/0.49$ mm and $0.12^\circ/0.95^\circ/1.85^\circ$ for the dipole fit. The dipole moments were $1,325/1,326/1,327$ nAm for each position showing consistency with the ground truth. For the moving phantom experiment without matrix coils active, the source reconstructed from data collected in Position 1 (maximum field offsets for channel shown in Figure 7.5c were <160 pT) localised to the same voxel as the ground truth with a change in orientation of 0.04° , compared to a change of 0.27 mm and 0.17° for the dipole fit. The source reconstructed from data collected in Position 2 (maximum field offsets were between $1,700$ and $2,350$ pT) was 4 mm away from the ground truth with a change in orientation of 3.16° , compared to a change of 0.95 mm and 1.37° for the dipole fit. The source reconstructed from data collected in Position 3 (maximum field offsets were between $3,230$ and $3,620$ pT) was 5.7 mm away from the ground truth with a change in orientation of 7.06° , compared to a change of 1.5 mm and 3.45° for the dipole fit. The estimated dipole moments for each position were $1,321/1,289/1,260$ nAm. Figure 7.6 shows the difference between the ground truth measurement and the sources reconstructed from data in Positions 2 and 3 during the experiment in which the matrix coil was off. Results show greater changes in source orientation, position and dipole moment from the ground truth for the experiment in which the matrix coils were not active, but the helmet was moving, highlighting the benefits of compensating field changes to ensure accurate source reconstructions.

Chapter 7 | Enabling ambulatory movement in wearable
magnetoencephalography with matrix coil active magnetic shielding
7.5 Results

	Beamformer		Dipole Fit		
	Distance from ground truth to estimated source (mm)	Angle between ground truth and estimated source (°)	Distance from ground truth to estimated source (mm)	Angle between ground truth and estimated source (°)	Estimated Dipole moment (nAm)
Ground Truth Recording	n/a	n/a	n/a	n/a	1,324
Static: Coils ON	0 (Same voxel)	0.05	0.067	0.046	1,324
Moving: Coils OFF Position 1	0 (Same voxel)	0.04	0.27	0.17	1,321
Moving: Coils OFF Position 2	4 (1 voxel)	3.16	0.95	1.37	1,289
Moving: Coils OFF Position 3	5.7 (2 voxels)	7.06	1.5	3.45	1,260
Moving: Coils ON Position 1	0 (Same voxel)	0.29	0.16	0.12	1,325
Moving: Coils ON Position 2	0 (Same voxel)	0.93	0.27	0.95	1,326
Moving: Coils ON Position 3	0 (Same voxel)	1.54	0.49	1.85	1,327

Table 7.3: Effects of helmet movement through non-zero background field on phantom source reconstruction accuracy.

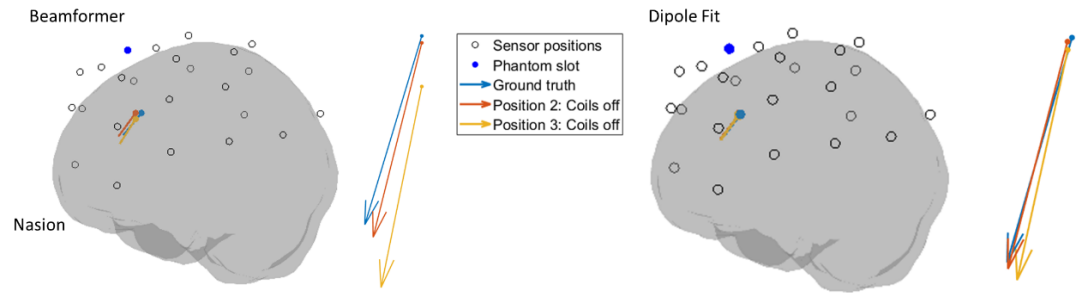


Figure 7.6: Dry phantom source reconstruction results. The reconstructed source position and orientations are shown for the dipole fitting and beamformer analysis for three cases, black circles show OPM positions and the blue dot highlights the slot into which the phantom was inserted. The first case is when the helmet was static and the matrix coils were switched off, referred to here as the ground truth. In the beamformer analysis, this voxel and approximate source orientation were consistent with the ground truth for all experiments other than trials in positions 2 and 3 during the experiment where the helmet was moving without the matrix coils active. Inset arrows show zoomed in source positions and orientations for comparison between conditions.

7.6 MEG Demonstration

To further demonstrate the capability of the matrix coil system we performed a MEG recording on a participant undergoing ambulatory motion. An array of 33 triaxial OPMs (99 channels) were arranged in the helmet to cover left and right sensorimotor regions. The participant (same participant as in Section 7.5.2) stood at the centre of the coil system wearing the helmet and holding two button boxes. After hearing an auditory cue indicating either ‘left’ or ‘right’, the participant continually pressed a button using either their left or right index finger until a second auditory cue (after 2 seconds) instructed the participant to ‘stop’. We expected this experiment to induce a movement related desynchronization and post-movement rebound in the beta band (13-30 Hz) in the contralateral sensorimotor cortex. The process was repeated 60 times, including 30 trials for each hand. Left/right trials were presented in a random order. During the experiment the participant was unconstrained and instructed to walk (exploring only the volume between the coils). The process was repeated with and without the matrix coil system active. The experiment was approved by the University of Nottingham Medical School Research Ethics Committee, the volunteer gave informed consent. For the experiment without the matrix coils, the OPMs were again operated in their 0.33x gain mode.

7.6.1 Sensor level and movement analysis

Figure 7.7a shows histograms of the translations of the centre of mass of the helmet recorded by the optical tracking system with (blue bars) and without (red bars) the matrix coil active. Figure 7.7b shows histograms of the rotation

about the centre of mass of the helmet recorded by the optical tracking system during the two experiments. In the coils-on condition the participant turned their back relative to their starting position resulting in a larger range of rotation values, this movement was not attempted during the coils-off condition as it would have produced field changes that exceed the maximum measurable field of the OPMs. Figure 7.7c shows histograms of magnetometer data collected in the two conditions. The absolute maximum change in field is reduced from >5.00 nT (saturation of some OPM sensors occurred during the recording) to 1.17 nT using the matrix coil system. Despite a similar range of movement, the matrix coil reduces the size of artefacts in the data, ensuring the sensors stay within their operational range and that gain changes are minimised.

7.6.2 Source reconstruction

We used the same beamformer analysis detailed in the previous section for this data. Here, co-registration of the sensor positions to an anatomical MRI of the participant was achieved using optical methods (Hill et al., 2020; Zetter et al., 2019). No regularisation was applied to the covariance matrices. The significant movement artefact and coil artefacts made ‘bad trial’ identification challenging, but one trial was rejected from the coils-off dataset where some sensors appeared to briefly malfunction.

To generate an image of the spatial form of neuronal activity in the beta band during the experiment, we first filtered the OPM dataset between 13 and 30 Hz (using fourth order, Butterworth filtering). Images of activation that show the pseudo-T-statistical contrast between activity in active and control windows were produced for left and right trials separately. Pseudo-T-statistics were computed at the vertices of a regular 4 mm grid spanning the whole brain of the participant. The active window was chosen to be 1 to 3 seconds following the start cue (i.e. during the button pressing) and the control window was chosen to be 3 to 4 seconds (contrasting the desync and rebound periods to maximise the pseudo T value). The grid of T values was thresholded to 80% of the peak value and overlaid onto the anatomical MRI of the participant. For Left (Figure 7.8a) and Right (Figure 7.8b) conditions with the matrix coils active and the corresponding Left (Figure 7.8c) and Right (Figure 7.8d) conditions without the matrix coil, Figure 7.8(i) shows the activation images from the experiment performed with the matrix coils active. The activity peaks in the contralateral motor regions during the button pressing as expected. Similar activation images are obtained with and without the nulling, though we note that the spread of measured fields shown in Figure 7.7 is sufficient to induce sensor gain changes in some data.

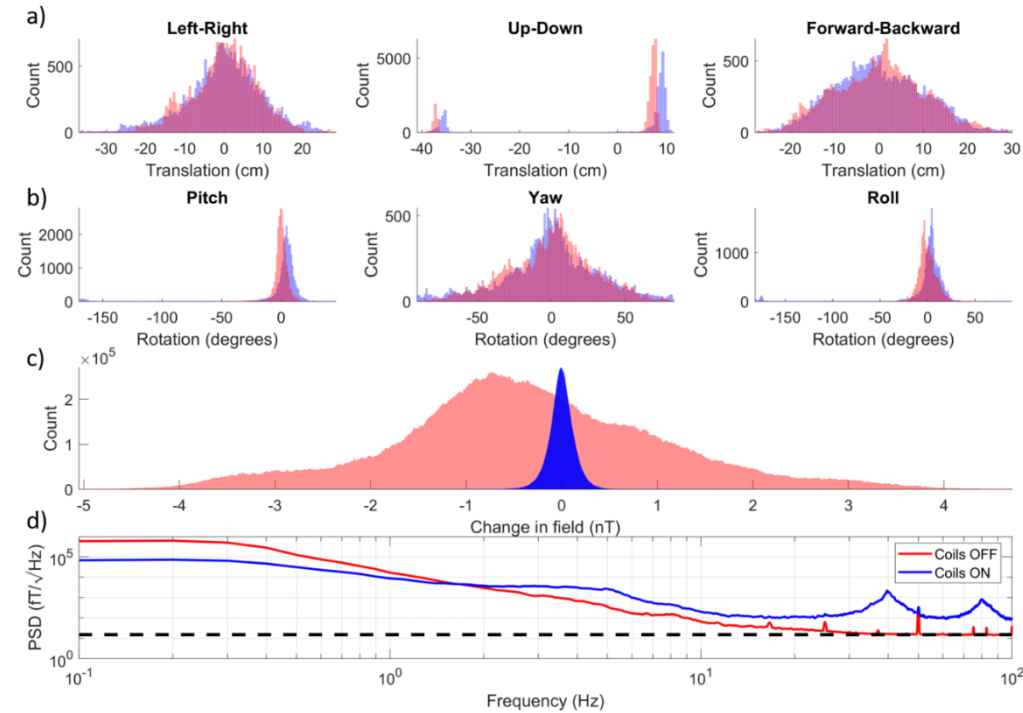


Figure 7.7: Range of motion and magnetic field change recorded from a participant undergoing ambulatory movements. a) Histograms of the change in position of the centre of mass of the OPM-MEG helmet relative to its mean position. The three histograms show left-right, up-down and forward-backward movement, respectively. For all plots, blue and red denote the experiments with and without the matrix coils active. **b)** Histograms of the change in orientation of the centre of mass of the OPM-MEG helmet relative to its mean orientation. The three histograms show pitch, yaw and roll, respectively. We note that only a short amount of time was spent at the large pitch and roll orientations, and there is a correspondingly low count rate at the extremes of the corresponding histogram x-axis. **c)** Histogram of the change in magnetic field measured by each channel of the OPM array relative to the value at the start of the recording. This shows that the matrix coil significantly decreases field variations which are induced by sensor movement. **d)** The power spectral density of the data measured by the OPMs in each recording. Compensating large field changes induced by participant movement results in a further increase in both the broadband noise and the 40/80 Hz coil artefacts. The black dashed line indicates 15 $\text{fT}/\sqrt{\text{Hz}}$.

The signal at the peak location of each image was reconstructed to form a virtual electrode timecourse, with beamformer weights now calculated in the broad-band by filtering data between 1–150 Hz. This virtual electrode was used to generate a time-frequency spectrum (TFS) by filtering the timecourse sequentially into overlapping frequency bands. For each band, the Hilbert envelope was calculated before averaging over trials and concatenating in the frequency domain. A control window of 7 to 8 seconds after the cue to commence button pressing was used to show change in activity relative to baseline. Figure 7.8(ii) shows the TFS for the left and right conditions displaying the expected desynchronisation and rebound in beta activity. Finally, virtual electrodes calculated using the full triaxial dataset of 99 channels and separately by using only the component of magnetic field which is radial to the surface of the head (33 channels) were compared to show the effectiveness of the triaxial beamformer in compensating artefacts. The power spectral density of the virtual electrode (across all trials) was computed and plotted for the two conditions in Figure 7.8(iii). As expected, the triaxial array is better able to differentiate the broadband noise and the 40 Hz artefact (and its 80 Hz harmonic) from neuronal sources compared to only the radial field. This is because the full vector field measurements enable more information to be gained on the spatial signature of interference (Brookes et al., 2021; Rea et al., 2022; Tierney et al., 2022).

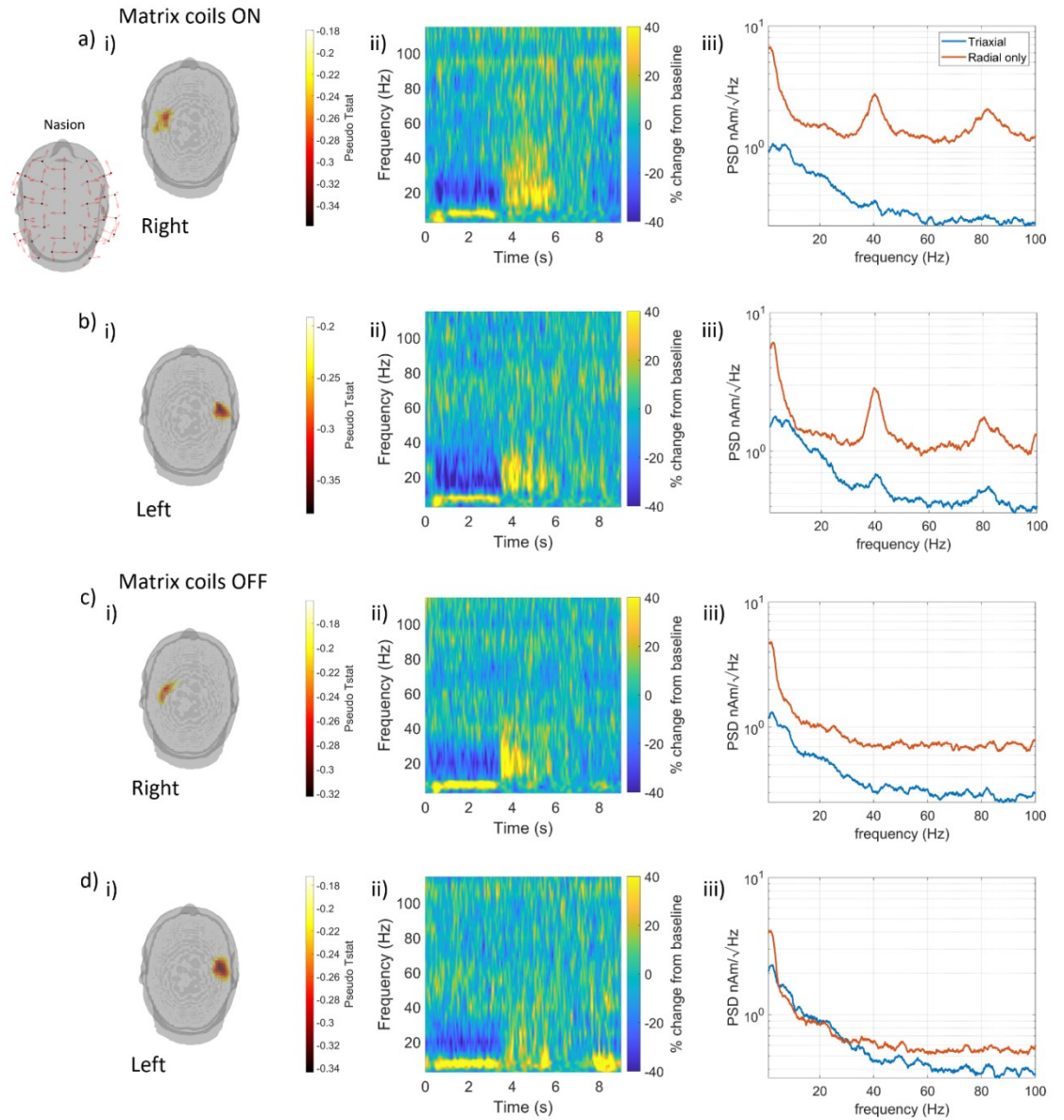


Figure 7.8: Source reconstruction of MEG data collected from a participant undergoing ambulatory movements with and without matrix coils active. a) Data from trials in which the participant was pressing the button with their right index finger with the matrix coil active. **b)** Data from trials in which the participant was pressing the button with their left index finger with the matrix coil active. **c)** and **d)** show data from right and left-handed trials during the experiments where the matrix coil was off. **For each case: (i)** Beamformer images of the spatial signature of beta band modulation (thresholded to 80% of the maximum value) shows activity in the contralateral sensorimotor cortices as expected (channel positions (black dots) and orientations (red arrows) shown in **a)**). **(ii)** Time-frequency spectra of a virtual electrode at the peak of the beamformer image showing movement related desynchronization (blue) in the beta band and post movement beta rebound (yellow). **(iii)** Power spectral density of the virtual electrodes reconstructed using a triaxial beamformer and a radial-only beamformer. Note how the triaxial beamformer significantly reduces the impact of the 40 and 80 Hz artefacts generated by the matrix coil.

7.7 Discussion

The matrix coil is a flexible, reconfigurable, active magnetic shielding system with application to fixed and moving arrays of magnetic field sensors. The shielding framework outlined here can be readily adapted to any coil system. Application to OPM-MEG in particular shows that high-quality source data can be collected from participants undergoing ambulatory motion. Unconstrained movement during a scan opens a wealth of possibilities for clinical investigation and allows a fundamentally new range of neuroscientific experiments. The framework adopted here could also be expanded to simultaneously null magnetic fields over multiple helmets, facilitating MEG studies of social interaction (King-Casas et al., 2005; Leong et al., 2017; Montague et al., 2002).

As highlighted in Chapter 3, exceeding the dynamic range of the OPMs can make their voltage response non-linear. Therefore, although data could be recorded during the MEG experiment conducted with the coils switched off, the effect of such errors in the error gain can lead to unreliable data recordings, which further emphasises the benefits of field nulling using a coil system (Boto et al., 2018; Iivanainen et al., 2019a). The sensor response may also be affected by magnetic field changes along axes orthogonal to the measurement axis (see Section 3.13). As shown by Borna et al., 2022, these cross-axis projection errors (CAPEs) can negatively affect source localisation, reducing the accuracy of spatial localisation of the source position and removing a key advantage of MEG (Nugent et al., 2022). To minimise CAPE, the authors suggested that field changes should be restricted to ± 1 nT (as was effectively achieved here). As previously mentioned, closed-loop operation of OPMs (where fields are continually applied to the internal coils) could help address this issue. However, closed-loop operation is also affected by CAPEs if it is not applied to all three axes. Precision control of the magnetic field environment is therefore crucial for OPM-MEG.

However, several technical issues need to be addressed to fully realise the potential of the matrix coil system if it is to become a standard technique. The available nulling volume must be expanded to allow for a greater range of motion; this could readily be achieved by mounting coils on the walls of the MSR (Holmes et al., 2022) and applying the framework established here. Such a design is discussed in detail in the following chapter. Although they can be corrected with post-processing and source reconstruction, the matrix coils produce both an increase in broadband noise above 1 Hz, and large drive frequency artefacts at 40 and 80 Hz which effects sensor level data. An increased nulling rate would not only improve system performance to address more rapidly varying fields but could also potentially shift the artefact outside the OPM bandwidth (via multiple updates at the same helmet position). Integration with improved hardware such as FPGA controllers should alleviate the problem. Narrowing the artefact peak and shifting it (e.g. such that it overlaps into the powerline artefact or is >100 Hz) may also help minimise its impact.

Cancellation of higher order field variations should also be considered; though the magnitude of the required coil currents will increase so coil driver specification and the impact on noise levels in the MSR must be evaluated.

The matrix coils, the method of production of spherical harmonic fields and the shielding framework adopted here could also have application outside MEG. For example, in designing excitation fields for large magnetic induction tomography systems (Cubero et al., 2020; Kim et al., 2019); adaptive nulling for atom interferometers for gravity sensing (Hobson et al., 2022); reducing systematic errors as mobile atom interferometers are deployed in real-world environments (Wu et al., 2019) and for fundamental physics experiments including very long baseline atom interferometry (Wodey et al., 2020) and measurements of the electric dipole moment of the neutron (Afach et al., 2014).

Overall, the matrix coil goes a long way to achieving one of the key benefits of OPM-MEG: unconstrained movement during a scan. As systems continue to develop, and the range of allowed experiments continues to expand, OPM-MEG has significant potential to become the method of choice for functional neuroimaging.

Chapter 8 Determining sensor geometry and gain in a wearable MEG system

8.1 Abstract

Source reconstruction with OPM data depends on our ability to perform system calibration – that is, determining sensor locations and orientations relative to each other and to the participant’s anatomy, as well as the relationship between sensor output and the magnetic field (sensor gain). In contrast to conventional MEG, OPM placement can change from subject to subject. Here, we explore two methods for calibration, both based on generating well-characterised magnetic fields across a sensor array. Our first device (the HALO) is a head mounted system that generates dipole-like fields from a set of coils. Our second (the matrix coil (MC)) generates fields using coils embedded in the walls of a MSR. Results show that both methods offer an accurate means to calibrate an OPM array (e.g. sensor locations within 2 mm of the ground truth) and that the calibrations produced by the two methods agree strongly with each other: reconstructed positions, orientations and gains differ on average by 2.0 mm; 1.2° and 1.3% between HALO and MC. When applied to data from human MEG experiments, both methods offer improved signal-to-noise ratio after beamforming suggesting that they give calibration parameters closer to the ground truth than presumed physical sensor coordinates and orientations. My contributions to this work include study conceptualisation, matrix coil calibration and data acquisition and processing for both the HALO and matrix coils experiments. The content of this chapter was recently accepted for publication in *Imaging Neuroscience*, where I am included as joint first author. Additionally, this chapter has been expanded to include my work on active shielding with the MC, which is not contained in the publication.

8.2 Introduction

Despite their promise, OPMs still have fundamental challenges to overcome prior to becoming mainstream MEG technology. One key challenge is array calibration, which for MEG applications includes defining the location of sensors (relative to each other), the precise orientation of the sensitive axis, and the relationship between the (voltage) output of the sensor and the magnetic field that passes through the cell (the sensor gain). Previously, in Chapter 4, we saw how accurate knowledge of these three parameters is essential for effective spatial filtering and source reconstruction. Errors in any of these calibration metrics can lead to significant degradation in the quality of the reconstructed neural activity.

In a SQUID-based MEG system, the calibration coefficients are set during system construction/installation, typically via the use of known magnetic fields from electromagnetic coils placed either inside or outside (Li et al., 2016) the system. Calibration accuracy depends on, for example, the tolerance of superconducting windings and their (fixed) placement within a cryogenic dewar, as well as deviations between the mathematical model of the field produced by the calibration coil and the actual field produced by the coil. Techniques such as spherical harmonic model-refinements (Chella et al., 2012; Taulu et al., 2005), taking X-Ray CT scans of coil wire paths (Oyama et al., 2022), and using larger coils to reduce field model errors (Adachi et al., 2023) can be used to improve accuracy.

In OPMs, however, calibration is more challenging. At the simplest levels, this is because the relative position and orientations of the sensors can vary from subject to subject. For example, when switching sensors between different rigid helmets. However, calibration is further complicated by the physics of OPMs, which can cause changes in both gain and orientation sensitivity. Specifically, calibration of an OPM depends on three key factors: (1) manufacturing tolerances, (2) factory-programmed sensor operational settings, and (3) local operating conditions. **Manufacturing tolerances** include the placement of the on-sensor coils with respect to the vapour cell, the homogeneity and orthogonality of the fields these coils generate, the propagation direction of the laser beam(s), the position where the vapour cell and the laser beam intersect, the laser beam diameter, polarisation, and intensity, and vapour cell characteristics (such as buffer gas pressure). **Operational settings** include the relative phase and frequency of the modulation field produced by the on-sensor coils, the exact lock-in demodulation procedure, the vapour cell temperature, the algorithm used to zero the field within the vapour cell and the laser wavelength offset settings; all of which result in light shifts and other Rubidium density factors that induce asymmetries in the resonance lineshape. **Local sensor operating conditions** include temporal field drift and varying background magnetic field and gradient field profiles between sites (Hill et al., 2022) which can introduce cross-axis projection errors (Borna et al., 2022) that strongly impact the orientation of the sensitive axis, and the sensor gain. Sensor age and intentional (or unintentional) changes in sensor firmware or settings also have an effect. Previous generations of OPMs have used factory based operational settings to minimise errors. However, the work presented here suggests this is inherently unreliable. Sensor positions, orientations, and gains should be independently determined during each MEG experiment to identify any deviations in sensor behaviour. Such an approach also allows for sensor locations and orientations to change from scan-to-scan (e.g. when using a flexible helmet).

In this chapter, a newly developed 192-channel miniaturised integrated OPM-MEG system is employed (Schofield et al., 2024), featuring sensors operating ‘as is’ directly from the factory floor (i.e., with no attempts made to

optimise performance) and we introduce two independent means of calibration – both based on generation of well-characterised magnetic fields over the OPM sensor array. Our first method uses a helmet-mounted planar disc containing dipolar coils called the ‘HALO’ (QuSpin Inc.); our second method uses a matrix coil (MC) magnetic field nulling system (Holmes et al., 2023b) (similar to work by Iivanainen and colleagues (Iivanainen et al., 2022) to perform similar calibrations). We aimed to show that we can accurately determine sensor locations, orientations and gains, and in this way calibrate all sensors in an array.

The calibration was tested by setting up the array in a rigid helmet and quantitatively comparing the HALO- and MC-derived sensor locations, orientations, and gains to those obtained from the computer aided design (CAD) model of the helmet and presumed factory settings. The calibration coefficients are tested for robustness using multiple measurements with the same technique. Further, both independent calibration methods are compared against each other. Finally, a series of MEG experiments were undertaken with human participants, testing the hypothesis that the accuracy of mathematical modelling of MEG data will increase following calibration (using both calibration systems).

8.3 Methods

8.3.1 OPM-MEG system

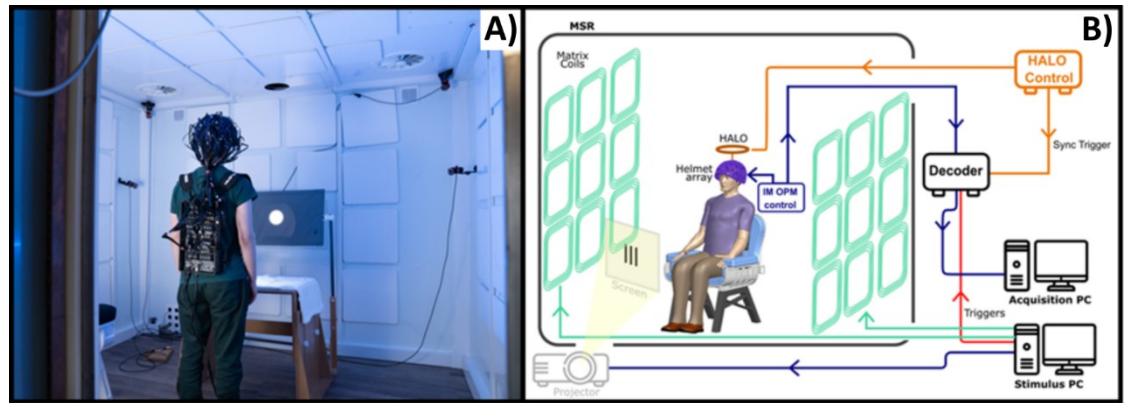


Figure 8.1: OPM-MEG system: A) The integrated miniaturised electronics system formed as a backpack which can be worn by the subject. The white square MC panels can be seen on each face of the MSR. B) System schematic.

The same OPM-MEG sensors as described in the previous chapter were utilized, consisting of 64 triaxial QuSpin sensors providing data from 192 independent channels. Again, the sensors were mounted in a 3D-printed helmet (Cerca Magnetics Limited, Nottingham, UK) which offers approximately even coverage of the cortex. The helmet is designed using CAD and constructed using

3D-printing, so the assumed locations of the vapour cells in each sensor are known (in principle) to an accuracy of ± 1 mm. Sensor orientations are assumed to be perpendicular to the OPM housing and are therefore known (in principle) to $\pm 1^\circ$. [In what follows we use this CAD-derived information to compare our calibration methods, however we emphasise that none of the assumed information was used for informing either calibration method. This means calibration is not only sensor-specific but also scan-specific if OPM-MEG data are acquired using a flexible helmet].

As detailed in Section 3.16 control of the OPM requires circuitry and associated software to stabilise the cell and laser temperatures, identify and lock the laser wavelength to the D1 resonance, zero the magnetic field within the cell, generate modulation fields and read out signals from the photodetectors (which are modulated at the same frequency as the modulation fields, and captured using lock-in-detection). In contrast to the previous setup, control of these processes was achieved using an integrated miniaturised electronics unit (see Schofield et al., 2024) (Figure 8.1A) (“*NEURO-1*”, QuSpin, Colorado, USA). The electronics unit is 36 x 20 x 6 cm in size, weighs 1.8 kg and can be worn as a backpack to enable (for example) ambulatory studies (Figure 8.1A). Each sensor head was connected to the backpack by a ribbon cable (2.2 gm^{-1} and 90 cm in length) and each sensor is controlled by a separate electronics card. These cards are grouped together in modules of 8. The digitised output of each sensor/module is sent to a multiplexer and then to a network card which passes all data, via ethernet, to a decoder (DAQ – sbRIO9637, National Instruments). The decoder integrates the sensor outputs with peripheral signals (e.g., those carrying the timings of the experimental paradigm) and passes everything to an acquisition PC, via a second ethernet connection. It is noteworthy that the electronics also enables three-axis closed-loop sensor operation, enabling a large dynamic range (currently ± 8 nT). However, closed loop operation was not required for the work described here due to low magnetic field drifts (Hill et al., 2022). The bandwidth of the OPMs is 0 – 135 Hz (where the upper limit represents a 3 dB loss in sensitivity).

As shown in Figure 8.1A, the MSR was equipped with the MC (Holmes et al., 2023b, 2022). This comprised coil elements attached to the inner walls of the MSR. These elements can be independently energised using low noise current drivers (Magnetic Shields Limited, Kent, UK) such that the field from all elements sums to flexibly create controlled magnetic field patterns within the MSR (this system will be described in more detail below). Illustrated in Figure 8.1B, a single ‘acquisition’ computer was used for OPM-MEG data acquisition. Experimental paradigms (along with associated triggers) and the MC were controlled by a second ‘stimulus computer’.

8.3.2 Calibration with HALO

The “HALO” comprised a circular printed circuit board (PCB) containing 16 independently controllable electromagnetic coils. Not only are PCBs cost-effective, but they can also be manufactured with a high accuracy, critical for use in calibration. Each coil was formed from 6-layers of a 45-turn planar spiral (270 turns total), with an inner radius of 3.68 mm and an outer radius of 10.94 mm. Within a single coil, each spiral layer was connected in series with the other layers by PCB vias. The coil radius was chosen such that when energised at a distance 5-10 cm from a sensor the coil creates a field that closely resembles a magnetic dipole. (Note that the large number of turns and layers means a small current can be applied, and so the relative contribution of stray field from the cables feeding current to the coil is minimised). 12 of these dipolar coils were equidistantly spaced (every 30°) around a circle of radius 12.7 cm; a further 3 dipoles were spaced at 120° intervals around a circle of 6.3 cm radius; the final dipole was placed at the centre of the circle (see Figure 8.2 (left)). This layout was chosen such that the system generated fields approximately evenly across the head. The HALO was electrically coupled to a driving circuit (QuSpin Inc.).

The procedure for running the HALO was as follows. First, the HALO was mounted in the OPM helmet on a base which holds the disc 5 cm above the helmet, as shown in Figure 8.2 (right). Following this, the door to the MSR was closed and the room demagnetised. Each of the 16 dipoles was sequentially energised, to create 16 (spatially different) dipolar field patterns across the sensor array. The driving circuit generated a 10 Hz oscillating current which was applied to one dipole for 1 s before being switched to the next dipole. Once all 16 dipoles had been energised the current was turned off. One limitation of dipoles is that the magnetic field falls very rapidly with distance, and so whilst nearby OPMs see a large field, distal OPMs see a small field. To overcome this, the sequence was run 4 times with dipole moments of 4 μAm^2 , 11.8 μAm^2 , 28.3 μAm^2 and 41.0 μAm^2 with a 5-s break between sequences. The procedure lasted ~90 s and OPM data were collected throughout.

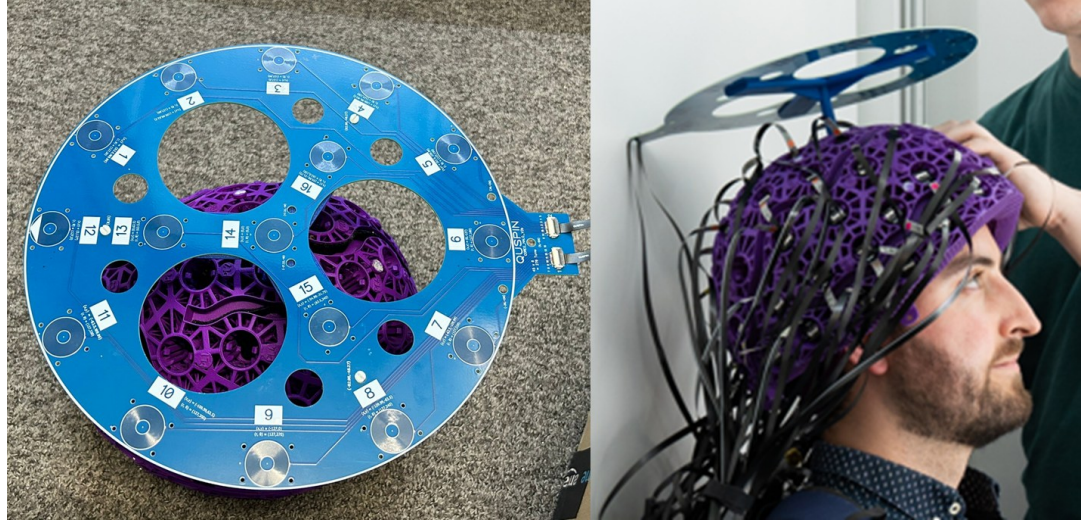


Figure 8.2: HALO calibration system: *Left)* Aerial view of the HALO. The system contains 16 independently controllable magnetic dipoles which make spatially distinct field patterns across the OPM array. *Right)* The HALO in position in the rigid OPM-MEG helmet being worn by a participant.

An algorithm was generated to calibrate each OPM based on the model of the field generated by the HALO. Assuming dipole n , is at location $\mathbf{p}_n$ relative to the centre of the HALO and that a sensor is located at $\mathbf{r}$ (also relative to the centre of the HALO) and makes a single measurement along an axis defined by the unit vector $\hat{\mathbf{o}}$. The sensor measurement, $V_n(\mathbf{r}, \hat{\mathbf{o}})$ (i.e. in volts), can be modelled by the equation

$$V_n(\mathbf{r}, \hat{\mathbf{o}}) = g \left\{ \frac{\mu_0}{4\pi} \left[\frac{3(\mathbf{r} - \mathbf{p})(\mathbf{m} \cdot (\mathbf{r} - \mathbf{p}))}{\delta^5} - \frac{\mathbf{m}}{\delta^3} \right] \cdot \hat{\mathbf{o}} \right\}. \quad [8.1]$$

Here, $\mathbf{m}$ is the magnetic dipole moment (whose orientation is perpendicular to the plane of the HALO, and magnitude is assumed to be the same for all dipoles), $\delta = \|\mathbf{r} - \mathbf{p}\|$ is the Euclidean distance from the coil origin to the measurement location, $\mathbf{r}$. g represents the sensor gain (in units of V/T). This equation allows us to model the fields generated by any dipole in the HALO, at any location and orientation across the array. A single sensor makes three measurements of field ($[V_{n\hat{\mathbf{o}}_1}, V_{n\hat{\mathbf{o}}_2}, V_{n\hat{\mathbf{o}}_3}]$ which represent the field magnitude along three axes, $\hat{\mathbf{o}}_1$, $\hat{\mathbf{o}}_2$ and $\hat{\mathbf{o}}_3$). By measuring field from all 16 dipoles, a single sensor makes 48 separate field measurements, and this is repeated 4 times (due to the 4 different dipole amplitudes) making a total of 192 measurements per sensor. By fitting these values to a model generated by the repeated use of Eq. 8.1, it becomes possible to determine the free parameters comprising the sensor location ($\mathbf{r}$), the 3 measurement orientations ($\hat{\mathbf{o}}_1$, $\hat{\mathbf{o}}_2$ and $\hat{\mathbf{o}}_3$), and the 3 gains (g_1 , g_2 and g_3). (In practice we defined orientation vectors such that their magnitude represented the

gain and the normalised unit vector is the orientation, hence only 12 free parameters are needed not 15). This offers a complete calibration of an OPM.

In practice, for each signal, the amplitudes and direction of the measured signals (relative to the phase of the coil current) were estimated via a fast Fourier transform. To avoid the problem of signals being too small in distal sensors, or so large in proximal sensors that cross-axis projection error (CAPE) effects and sensor gain errors would confound the calibration, only segments of data where the measured 10 Hz signal was between 1 pT and 1,000 pT in amplitude were used in the fitting algorithm. The fitting procedure was implemented in MATLAB using the 'fmincon' function, which minimises the sum of the squared differences between the dipole model (of fields generated by the HALO) and measured data in such a way to determine the optimum sensor location, orientations and gains. The initial guess for the sensor position was the same for each sensor and was approximately the centre of mass of the helmet. The initial channel gain was set to the assumed 2.7 V/nT and each channel orientation was set in the front-back direction of the helmet. [Note – as discussed in Section 3.16 the two laser beams, and hence the precise locations of the field measurements for the x and z field components are offset from one another by $\sim 600 \mu\text{m}$. However, this small difference was ignored in the fitting algorithm].

8.3.3 Calibration with matrix coils

The MC comprises 94 independently controllable square coils of side length 450 mm arranged (approximately) symmetrically in 4x4 grids on each MSR face. (Due to access requirements, coils on the door face are arranged asymmetrically and 2 coils are removed on the face of the MSR opposite the door because a projector porthole blocks their positioning). We used the MC elements to generate known fields by which to calibrate the OPMs. However, to do this we need to know what field each coil element produces – this is termed the MC forward model.

8.3.4 Characterisation of the MC system

As described in the previous chapter, one could in principle use the positions of the wire paths of each coil to generate a forward model to ensure accurate knowledge of the fields generated by each MC element. However, interactions between the wire paths and the MuMetal walls of the MSR (Hammond, 1960; Roshen, 1990), complexities in monitoring many coil currents, and potential inaccuracies involved in mounting the coils means that simulating the field produced by each coil will not reflect the real system accurately enough for calibration. Here, we chose instead to use a data-driven approach similar to the one described in Section 5.3.2.3. Originally described by

Iivanainen et al., 2022, this calibration procedure also fits a spherical harmonic model to the fields generated by the coils, where real data is used instead of simulation results. Briefly put, Iivanainen et al., 2022 measured the fields produced from a system of 18 coils placed inside a cylindrical magnetic shield (MSC) over a volume containing an OPM-MEG helmet. A vector spherical harmonic model was then fit to the measured fields, thus obtaining a forward model describing the field generated by each coil, within a volume of interest, per unit of applied voltage. This approach has also been used to measure remnant fields inside MSRs (Holmes et al., 2022; Mellor et al., 2021; Rea et al., 2021a) and to model both neuronal and interference fields measured by MEG systems (Taulu and Kajola, 2005; Tierney et al., 2022, 2021).

To calibrate the 94 coils installed in the MSR, each coil was to be driven at a known frequency such that a measurement of the field magnitude and direction produced by each coil at a known position inside the MSR could be found via the Fourier transform of the data. Repeating the process at different points in a desired volume provides enough data to fit a spherical harmonic model. This model can then be used to for sensor calibration or remnant field cancellation. Recalling from Section 7.3, the currents $\mathbf{i}$ required to generate the desired field components $\Delta\mathbf{b}(t)$ are given by equation

$$\mathbf{i} = \mathbf{F}^+ \mathbf{B}_{mat}^\dagger \Delta\mathbf{b}(t). \quad [8.2]$$

where, as discussed, $\mathbf{F}^+$ is the pseudoinverse of $\mathbf{F}$, the matrix describing the strength of each field harmonic magnetic field component generated by each coil per unit current, and $\mathbf{B}_{mat}^\dagger$ is the pseudoinverse of the design matrix (model of the desired field at each target point).

The data required to estimate the calibration matrix $\mathbf{F}$ was obtained using a triaxial Bartington Mag-13MSL100 fluxgate magnetometer (Bartington Instruments, Witney, UK) integrated with an optical tracking system (Natural Point Inc., Corvallis, OR, USA). The fluxgate was connected to a National Instruments DAQ. Each coil was to be driven at a known frequency such that a measurement of the field magnitude and direction produced by each coil at a known position inside the MSR could be found via the Fourier transform of the data. For this, we used the MATLAB NI-DAQmx package function ‘readwrite’ to simultaneously generate and record signals with a sampling frequency of 10 kHz. Repeating the process at different points in a desired volume provides enough data to fit a spherical harmonic model, telling us how much each coil contributed for each field component per unit of applied voltage. The central volume is where the subjects’ heads are placed when they are being scanned with the OPM helmet. This was chosen as the initial calibration region so that field cancellation results could be compared against our previous biplanar coil system (Holmes et al., 2018a). We chose to sample a 40 x 40 x 40 cm³ volume in steps

of 10 cm on all three axes (125 points in total). Shown in Figure 8.3A, a small wooden table was built which could hold the fluxgate sensor in the centre of the room at different heights and positions.

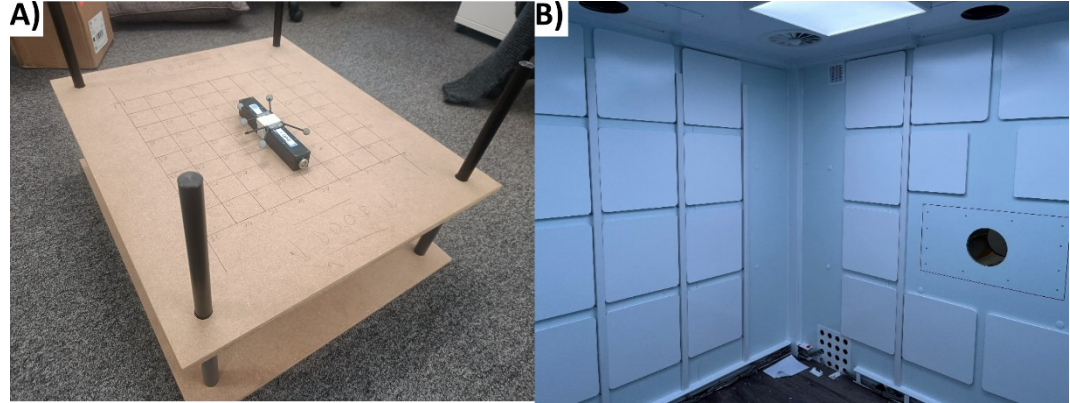


Figure 8.3: Experimental setup for calibrating the MC system. A) Wooden support with marked spacings employed to support the fluxgate at each point to the target volume. **B)** New matrix coils on the walls of the MSR in the Nottingham OPM-MEG laboratory.

Simultaneous activation of the coils required using different driving frequencies for each coil so they could later be identified in the Fourier transform. Consequently, we decided to measure how big an influence the driving frequency had on the field magnitudes being produced. As shown in Figure 8.3B, the coils are placed on all walls of the MSR, as well as the floor and ceiling. This means that they are in proximity with the Mu-Metal that make up the main shielding layers of the room. As described in Section 5.2, Mu-Metal has a high magnetic permeability and high electrical conductivity. Therefore, the magnetic fields produced by the coils will interact with the material in a frequency dependent manner. Additionally, the coil amplifier circuits were configured as voltage drivers, as the frequency of the voltage increases the coil current may decrease, an effect that could impact the accuracy of the calibration. The impact of these effects was quantified by sequentially activating each coil at 1 Hz then gradually increased the driving frequency in steps of 1 Hz up to 50 Hz. Plotting field amplitude as a function of the driving frequency (Figure 8.4A) shows a decrease in amplitude as frequency increases, producing changes of up to 5% or more in field magnitude suggesting a narrow frequency range would be required for accurate procedure.

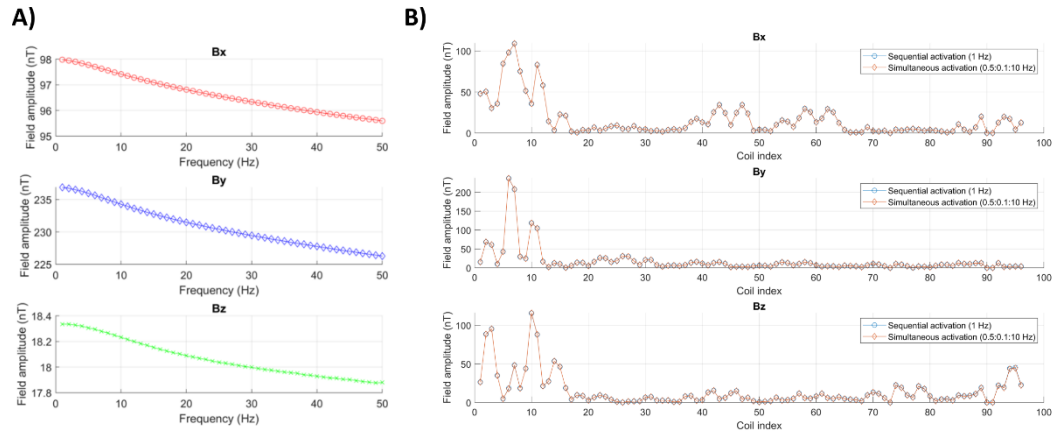


Figure 8.4: Preliminary results prior to calibration: **A)** Plots showing magnetic field magnitude versus driving frequency along each measurement axis for a single coil. **B)** Plots showing magnetic field magnitude for all coils when activated sequentially and simultaneously.

To address the frequency dependence, we chose frequencies between 2 and 11.5 Hz with a separation of 0.1 Hz, recording for 20 s for sufficient frequency resolution to resolve all peaks (such that peaks were clearly resolvable in the Fourier transform with resolution $1/20 \text{ s} = 0.05 \text{ Hz}$). This ensured that field magnitude changes due to different driving frequencies were below 1%. To verify the suitability of this range, each coil was then pulsed using a 20 s cosine wave with a 10 V amplitude. Magnetometer data were recorded simultaneously. Field amplitude values were obtained for each coil. Results for each axis are shown in Figure 8.4B, where no difference could be observed between simultaneous or sequential activation. Therefore, to carry out the calibration, the simultaneous activation approach was chosen for the final calibration experiment.

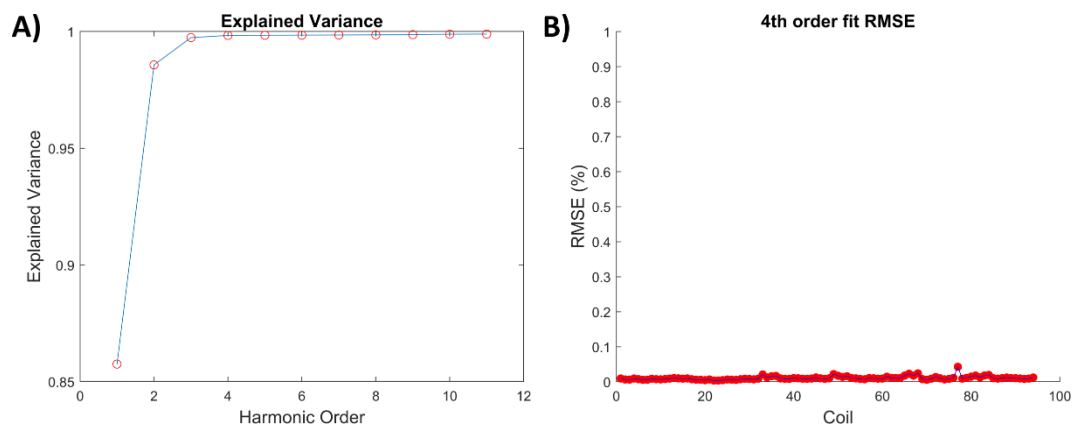


Figure 8.5: Spherical harmonic model fit results. **A)** Explained variance of the model when compared against measured data versus the model order used, for a single coil. **B)** Root mean squared error between the model and the measured field for all 94 coils.

Finally, the fields generated simultaneously by all coils were recorded at 125 positions in the target volume, moving the fluxgate after each 20 s pulse. The direction and magnitude of the field generated at each grid point by each coil was extracted. The resulting dataset was employed to fit spherical harmonic models of increasing order. The quality of the fits was quantified by comparing the modelled fields to the measured ones using metrics such as explained variance and root mean squared error (RMSE). Results for a single coil are shown in Figure 8.5A, demonstrating that a 4th order harmonic model was more than sufficient to accurately describe the fields produced. As shown in Figure 8.5B, the RMS error between the data and the model was <1% for all coils.

Finally, the ability to cancel out the background field with the newly designed matrix coils was tested against the previous active cancellation system, the biplanar coils (Holmes et al., 2018a). Figure 8.6B presents a histogram of the results for the central volume where the participants are normally seated in the MSR. Results demonstrate that the MC not only match the performance of the biplanar coils but also more effectively reduce the gradient components of the background field. The same technique was employed to null the field in a volume positioned above, to enable scanning of participants while standing (Figure 8.6C). The calibration process was performed in the same manner, measuring the fields generated by the coils in 125 in a “standing” volume. Results shown in Figure 8.6D demonstrate that the field cancellation was effective, achieving a sufficiently low field for high-quality imaging.

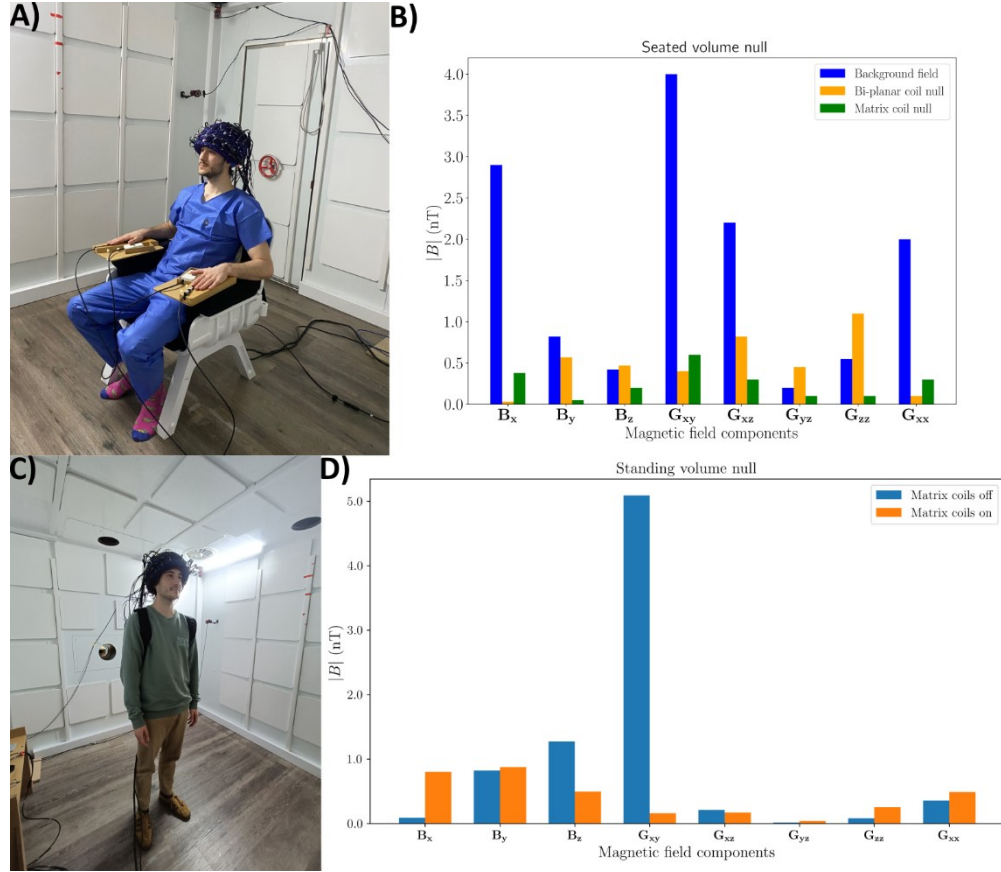


Figure 8.6: Field cancellation results: Photos A) and C) show where the participant was within the MSR to test field cancellation with the MC while seated and standing. The histograms B) and D) show the magnitude of each magnetic field component of the background field before and after the field cancellation was switched on for the seated and standing cases, respectively. Note that plot B) shows results for both the biplanar coil cancellation (orange) and the matrix coil cancellation (green).

8.3.5 OPM Calibration procedure

To calibrate the OPMs, we used the same signal used to derive the MC forward model, with a maximum field generated of around 1,000 pT. We took the FFT of the resulting OPM data, to quantify the field detected by the OPMs from each coil (based on the known coil frequencies) and minimised the difference between the measured data (v_n at channel n) and the forward model to determine sensor locations orientations and gains. Mathematically,

$$\min_{\mathbf{r}, \hat{\mathbf{o}}, g} \left\| \sum_{n=1}^N v_n - g \mathbf{B}_n(\mathbf{r}) \cdot \hat{\mathbf{o}} \right\| \quad [8.3]$$

for each channel. Here $\mathbf{B}_n(\mathbf{r})$ denotes the field from each matrix coil from the MC forward model. We reduced the number of coils used from 94 to 12 (2

randomly selected from each face) and set a (empirically derived) threshold level for optimisation and randomised the selected coils in the system until this threshold was met, or 100 iterations were completed (typically this indicated an inactive sensor or a channel with high noise). This was done as using all coils together made the system perform poorly, possibly as the initial search space is difficult to navigate with many coils. We again assumed in our minimisation that each of the channels in an individual OPM sensor shared the same location and optimised the three channels of each sensor simultaneously. The initial guess for OPM position was the centre of the grid used to map the coils, with the channels again oriented along the approximate front-back alignment direction of the helmet with 2.7 V/nT gain. We note that Iivanainen et al., 2022, first used their coils to generate three orthogonal uniform fields and the complete set of five field gradients to obtain an initial guess of the sensor orientation and then position before refining with the harmonic model as above. We found that this initial step was not needed after reducing the number of coils used in the minimisation. This may be due to the larger distance between our MC and the helmet (1.4 m) compared to their experimental setup.

8.3.6 Validation experiments

To validate our two calibration methods (HALO and MC), we undertook a series of experiments. For each experiment, the OPMs were located in the 3D printed helmet (Figure 8.1C). All sensors were used ‘as is’ from the production line (i.e., with no in factory calibration). This means that gain and orientation sensitivity are subject to errors from manufacturing tolerances and operational settings as well as local conditions. During the sensor start-up procedure, we used the manufacturer’s software to perform a “field zeroing” process, by which the on-board sensor coils were used to offset any remnant DC background field, ensuring a close to zero field within the cell for the experiment. The manufacturer’s software also carries out an additional step in which each of the three on-sensor coils is used to produce a field of known amplitude. Measurements of the amplitude and phase of the variation of transmitted beam intensity at the modulation frequency for the three different applied fields are then used to establish signal weightings that yield values of the field components oriented along the three orthogonal directions defined by the three sensor coil fields (which are approximately equivalent to the orientations of the sides of the sensor casing). These measurements are used to set the assumed sensor gain to 2.7 V/nT for all three axes. Following this, we performed our calibration procedures, as described above.

A single experiment comprised calibration with both the HALO and MC. This was repeated 11 times. For the first 5 repeats, the MSR was opened, and the HALO moved to a different position relative to the helmet (specifically it was positioned on the top, left, right, back and front of the helmet, as shown in Figure 8.7 and remained there throughout the experiment). For the remaining 6 repeats nothing was changed between experiments (and the HALO was sited on the top

of the helmet). The OPMs were always restarted between successive experiments. The order in which the HALO and MC calibration occurred was switched for each experiment.

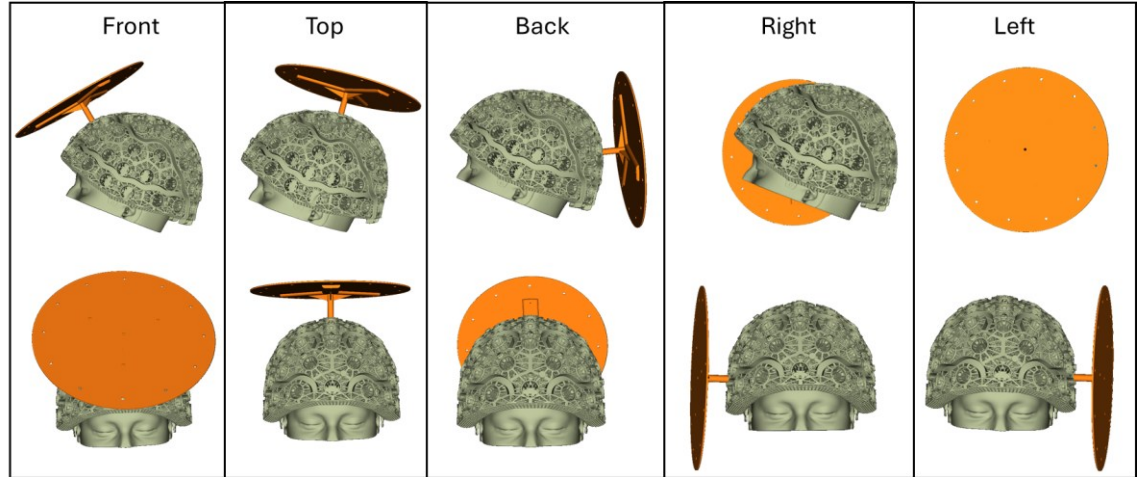


Figure 8.7: HALO positioning: All 5 locations the HALO was placed within the helmet.

Because the HALO was inserted into one of the sensor slots in the helmet. We had to remove one sensor from the helmet, and hence the calibration process. We also removed any sensors with excessive noise levels. This left us with seven datasets with 63/64 sensors, two datasets with 62/64 sensors and two datasets with 61/64 sensors. Calibration was also made complicated because moving the location of the HALO (which occupies one sensor slot) meant that we were not able to repeat the calibration for every possible sensor slot in the helmet, for every experiment performed. For this reason, some slots had more repeat experiments (ranging from 11 to 4 repeats).

Following data collection and fitting (using the procedures described above) for each of the 11 runs, we had two independent system calibrations (one from the MC array and one from the HALO), both comprising sensor locations, orientations and values of the gain for each channel. We quantitatively compared these data in three ways:

- 1) **Location:** The only ‘ground truth’ available was the locations of the cell for each OPM, which are known from a combination of the helmet CAD file and the design of the OPM. The accuracy of these values is limited by the manufacturing tolerance of the helmet and OPM, the precise location at which the laser passes through the cell (which we assumed to be the centre), and the extent to which all sensors are correctly inserted into the helmet. Nevertheless, we expect these CAD-derived locations to be accurate to within ~ 1 mm. Comparison of these values to the calibration-derived locations is somewhat complicated since the CAD locations are in the coordinate space of the helmet, and the calibration locations are in the

coordinate space of either the HALO or the MC. To quantitatively compare the two, we first computed the Euclidean distances from every sensor in the helmet CAD model to every other sensor. We repeated this calculation for the locations derived using both calibration methods and computed a matrix of residuals by taking the absolute value of the difference between the CAD-derived distances and the calibrated distances. We calculated the mean and standard deviation of these values for each sensor across experiments to form an estimate of the accuracy and repeatability of the location estimate for each sensor. In addition, we also used an iterative closest point (ICP)-style minimisation algorithm to find the rigid body transformation of the calibration-derived sensor locations to the corresponding CAD locations. The algorithm found the transform which minimised the mean Euclidean distance between CAD and calibration-derived locations. We then took the final mean Euclidean distance as an *absolute* value of the difference between the calibration and CAD-derived locations. (Note that it would also have been possible to generate a similar transform based on the known geometry of the helmet and the HALO; however, this method was not used as it was felt the ICP-like approach would lead to a lower overall error).

- 2) **Orientations:** The assumed sensitive orientation of OPM measurements relates to the modulation field directions, which in turn depend on the orientation of the on-board sensor coils. These orientations should point along the axes of the casing of the OPM (see Figure 8.1A). We again used the ICP algorithm to rotate/translate the calibration-derived locations to the CAD locations. We then compared the three orthogonal axes of the sensor casing (from the CAD) to the calibration-derived orientations for each sensor axis. Specifically, for all three axes and for all OPMs we measured the angle between the assumed axis and calibration-derived axis. We then compared both the stability of each method, and the agreement between methods, by calculating and plotting the mean and standard deviation across all available runs from HALO-derived angles against MC-derived angles. We reasoned that if both approaches were stable, the error-bars would be small for all axes (i.e., the angle difference similar for each run). We also reasoned that a linear relationship would suggest that the calibration methods were equivalent (i.e. we find the same sensor orientation with the HALO and the MC calibration).
- 3) **Gains:** The gain of each OPM channel is assumed to be set using the sensor start-up procedure. We therefore expected our recovered gains to be centred around 2.7 V/nT. We produced equivalent plots to those generated for the orientations to compare the stability of and agreement between methods.

8.3.7 Human experiments: data acquisition

We undertook a series of human experiments with the aim to determine whether calibration of the OPMs leads to an improvement in OPM-MEG performance when assessing data in source space. Seven healthy participants (2 identified as female, 5 identified as male, mean age 32 ± 7 years, all right-handed) took part in the study, which was approved by the University of

Nottingham Faculty of Medicine and Health Sciences Research Ethics Committee (approval number H16122016). All participants provided written informed consent.

All subjects underwent a visuo-motor experiment designed to elicit oscillatory responses in both the beta and gamma bands, as well as evoked responses. The experimental paradigm incorporated two types of trials:

- 1) **Circles trials:** A visual stimulus (a central, inwardly moving, maximum-contrast circular grating) was presented. The grating subtended a total visual angle of 14° and was displayed for 1.5 s. This was followed by a baseline period lasting 2 s, during which a central fixation cross was displayed. Whilst the circle was on the screen the subject was asked to make repeated abductions of their right index finger. There were 60 circles trials per experiment. This visual stimulus is known to induce gamma oscillations in visual cortex (Hoogenboom et al., 2006) whilst the finger movement is known to modulate beta oscillations in motor cortex (Pfurtscheller and Lopes da Silva, 1999).
- 2) **Faces trials:** In these trials a photograph of a face was displayed on screen for a duration of 0.3 s, followed by a (jittered) rest period of duration 1 ± 0.1 s (during which a central fixation cross was shown). A total of 180 faces trials was used. This task generates evoked responses in primary visual and fusiform areas (Bentin et al., 1996; Halgren et al., 2000; Hill et al., 2022; Taylor et al., 2001).

In all cases, visual stimuli were presented via projection through a waveguide in the MSR onto a back projection screen, positioned ~ 100 cm in front of the subject (using a ViewSonic PX748-4K data projector).

In an experimental session, the subject was first seated on a patient support at the centre of the MSR. The OPM helmet was placed on the subject's head, and the HALO was positioned on the top of the helmet (secured via an empty OPM slot – Figure 8.7 (top)). Following this, the door to the MSR was closed and the room demagnetised (this procedure takes <1 minute and reduces the remnant field inside the MSR to ~ 2 nT (Rea et al., 2021a)). The manufacturer field-zeroing and parameter setting was performed and then calibration of the OPMs was performed using both the HALO and the MC; this process took a total of 2 minutes. The experimental paradigm was then run, and OPM-MEG data collected at a sample rate of 375 Hz. The experimental paradigm lasted ~ 550 s and the total experimental time (including degaussing, calibration using both techniques, and the experiment itself) was ~ 13 minutes.

Immediately following MEG data acquisition, we used an optical scanning technique to determine how the helmet was positioned on the subject's head. Specifically, a 3D digitisation of the participant's head (with the helmet in place) was acquired using a 3D structured light scan (Einscan H, SHINING 3D, Hangzhou, China). The 3D surface of the subject's face was extracted from this scan and matched to the equivalent surface taken from a T1-weighted anatomical

magnetic resonance image (MRI). This enabled a co-registration of the helmet relative to brain anatomy (Hill et al., 2020; Zetter et al., 2018).

8.3.8 Data analysis

OPM-MEG data for every channel were initially inspected by computing the power spectral densities, and any channels with a high noise floor (taken as >30 fT/ $\sqrt{\text{Hz}}$ in the 60 – 80 Hz band) or very low signal levels (<7 fT/ $\sqrt{\text{Hz}}$) were removed. A trial-by-trial analysis was also carried out, whereby trials with variance greater than 3 standard deviations from the mean trial variance were automatically removed. Data were also inspected visually, and any obvious noisy channels or trials removed. A 1 – 150 Hz band pass filter was applied along with notch filters at the powerline frequency (50 Hz) and two of its harmonics.

We used a beamformer spatial filter (Robinson, 1999) to process data in source space. This requires accurately calibrated data, and we used 3 separate approaches:

- 1) **Assumed calibration:** Sensor locations were derived from the helmet CAD; the location of the helmet relative to the brain was derived from the structured light scan and MRI. The combination of these data allowed co-registration of sensor locations relative to the brain. The orientations were assumed to be orthogonal, and parallel to the sides of the sensor casing. The sensor gain was assumed to be 2.7 V/nT.
- 2) **HALO calibration:** We used the ICP algorithm to co-register the HALO-derived locations to the helmet CAD, and this coupled with the structured light scan and MRI allowed sensor locations relative to the brain to be derived. For every channel, the orientation and gain were taken directly from the HALO fitting algorithm (with orientations rotated to the same space as the MRI scan). Recorded voltage data for each channel were divided by the calculated gain value for each channel to yield field data.
- 3) **MC calibration:** This was identical to the HALO calibration but using MC-derived coefficients (locations, orientation, and gains).

Notice that for all three calibrations, the processes of co-registration were identical. Having calibrated the system in these three ways, a forward model was constructed using a single shell volume conductor model (Guido Nolte, 2003). Following this, we undertook three separate analyses:

Gamma modulation: Data collected during the circles trials were segmented to 0 s to 3.5 s windows (relative to the onset of the circle) and filtered to the 35 Hz to 55 Hz band. A covariance matrix and beamformer weights were constructed using these data. To make an image showing the spatial signature of stimulus induced gamma change, we contrasted 35-55 Hz oscillatory power in

the 0.5 s to 1.5 s (active) window to power in the 2.5 s to 3.5 s (control) window, deriving a pseudo-T-statistic (Vrba and Robinson, 2001) for all voxels on a regular 4-mm grid covering the brain. Source orientation for each voxel was taken as that with the largest signal power. Having derived the location of largest gamma change, we then constructed a ‘virtual electrode’ showing the timecourse of electrophysiological change at this peak location. This was done in two ways; first, we generated a gamma amplitude envelope timecourse by taking band-limited data for each trial, applying a Hilbert transform to get the analytic signal, and then taking the absolute value of the analytic signal and averaging over trials (this is termed the Hilbert envelope). Second, we recalculated the beamformer weights using broadband (1 – 150 Hz) data, and then constructed a time frequency spectrogram (TFS) by sequentially filtering data into overlapping frequency bands, deriving the Hilbert envelope for each band and concatenating these data in frequency. In both cases, an estimate of baseline amplitude was derived (independently for each frequency band) in the control window (3 s to 3.5 s) and this was subtracted; the data were also normalised by these same baseline values to give an estimate of change relative to baseline ‘noise’. Finally, gamma band signal-to-noise ratio (SNR) was measured as the change in mean gamma amplitude (between the active and control window) divided by the standard deviation of the envelope in the control window.

Beta modulation: Stimulus induced change in beta power (due to finger movement) was mapped in a similar way to the gamma change. Data from Circles trials were segmented into 6-s windows (starting at the onset of the circle stimulus), filtered into the 13 Hz to 30 Hz band, and covariance and beamformer weights calculated. A pseudo-T-statistical image was generated, contrasting active (1 s to 2 s) and control (2.5 s to 3.5 s) windows. A Hilbert envelope of beta amplitude and a TFS were derived for the location of maximum beta modulation as described above (but with a baseline window of 5 s to 6 s), and SNR was calculated as the difference in mean beta amplitude in the active and control windows divided by the standard deviation in the active window.

Evoked responses: To look at evoked responses to faces, data were segmented to -0.24 s to 1.26 s time windows (relative to the presentation of a face) and frequency filtered to the 2 Hz to 40 Hz band. Covariance and weights were constructed using data from all faces trials. To compute the evoked response, we first used a beamformer to reconstruct a virtual electrode at an anatomically defined point in the primary visual cortex (selected according to the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002)). Beamformed timecourses were averaged across trials, giving the evoked response. For the peak in the evoked response at 108 ms, we generated a pseudo-Z-statistical image (which contrasts beamformer projected source amplitude (at a single point in time) to the noise amplitude (Vrba and Robinson, 2001)). The instantaneous beamformer projected amplitude was normalised by an estimate of the projected noise (taken as $(\mathbf{w}^T \mathbf{C}_N \mathbf{w})^{1/2}$ where $\mathbf{w}$ are the beamformer weights and $\mathbf{C}_N$ is the 2 – 40 Hz covariance estimated in a control window (1.06

s to 1.26 s)). Evoked response SNR was estimated as the maximum amplitude of the evoked response divided by the same projected noise.

Each of the above three analyses was undertaken (independently) for each of the three calibration types (assumed (CAD), HALO and MC). We tested statistically (using Wilcoxon signed rank test) whether SNR was increased when using either the HALO or MC compared to the assumed calibrations. We also explored the source localisation repeatability by comparing the peak location for each participant in each method. To do this, we co-registered each subject to the MNI-152 average brain using FLIRT (FSL) (Jenkinson et al., 2002b; Jenkinson and Smith, 2001) and computed the average and standard deviation of the peak location across participants for each case. We then calculated an “error ellipsoid” (one for each calibration method) that was centred on the average location and with each axis of the ellipsoid representing the standard deviation of peak locations in X, Y, and Z across participants. We reasoned that if all three methods localised with similar accuracy, the ellipsoids would overlap with similar volumes (suggesting that errors are dominated by intersubject variation rather than calibration method).

8.4 Results

8.4.1 Validation experiments

Figure 8.8A shows the basic output of the calibration procedures. In both the left and right panels, the grey data-points and arrows show the sensor locations and sensitive orientations, according to CAD, respectively. In the left-hand plot, the coloured data-points and arrows show the HALO-derived locations and orientations following the ICP process. In the right-hand plot, the coloured data points and arrows show the MC-derived locations and orientations following the ICP process. In both cases, the colour of the arrow represents the derived gain multiplier for that channel (i.e., relative to the assumed value of 2.7 V/nT); blue shows gain scaling values <1 and red shows gain scaling values >1 . Note that grey arrows are used for the CAD data as we always assume a gain of 2.7 V/nT. Data from a single representative experimental run are shown. For this specific run, the mean (across sensors) *absolute* Euclidean distance from the CAD-derived to the HALO-derived sensor location was 2.9 mm; the equivalent distance from the CAD to the MC-derived location was 3.4 mm. Across all experimental runs, the average *absolute* Euclidean distances were 3.0 ± 0.1 for the HALO and 3.7 ± 0.3 for the MC (mean $\pm$ standard deviation values shown). These values show good agreement between calibration and the CAD (the latter being the closest we have to a ground truth).

A limitation with these absolute discrepancies is that they do not allow investigation of which sensor locations are best matched to the CAD-derived

locations. This is because our ICP algorithm minimises the average distance between CAD- and calibration-derived locations, and this could mask individual sensors that offer only a poor agreement to CAD. For this reason, we also derived sensor-to-sensor distances across the helmet (which are independent of the ICP algorithm). Figure 8.8B, C and D show matrices representing the residuals between the CAD-derived and the calibration-derived sensor-to-sensor distances. Figure 8.8B shows the comparison between the HALO and CAD. Figure 8.8C shows the comparison between the MC and CAD. Figure 8.8D shows the comparison between the HALO and the MC. Note first that the residual matrices in Figure 8.8B and Figure 8.8C appear visually similar (the Pearson correlation coefficient between these matrices is 0.77). This means that sensors in which HALO-derived locations differ most from CAD, also tend to be the sensors where the MC-derived locations differ most from CAD. In general, the residuals between the HALO and MC sensor-to-sensor distances were lower, suggesting that the HALO and MC are in better agreement with each other than they are with CAD. This suggests the dominant inaccuracies relate to the CAD itself (i.e. helmet manufacture and sensor placement).

Formalising the above results, we computed the average residual sensor-to-sensor distance across all sensors and all experimental repeats (i.e., the average value of all elements in the corresponding matrix Figure 8.8B, C or D) and computed an estimate of how much individual inter-sensor distances changed from repeat-to-repeat by averaging the individual standard deviation values (i.e., the average value of all elements in the corresponding matrix Figure 8.8E, F or G). The final values were 2.08 ± 0.61 mm for HALO vs. CAD; 2.62 ± 1.7 mm for MC vs. CAD, and 1.97 ± 1.5 mm for HALO vs. MC. (All cases show mean $\pm$ standard deviation.) Most importantly, these values, and the matrices from which they are derived, show that both of our calibration techniques are able to localise sensors to within a few millimetres of their CAD-derived locations, and that these residual ‘errors’ most likely derive from the CAD.

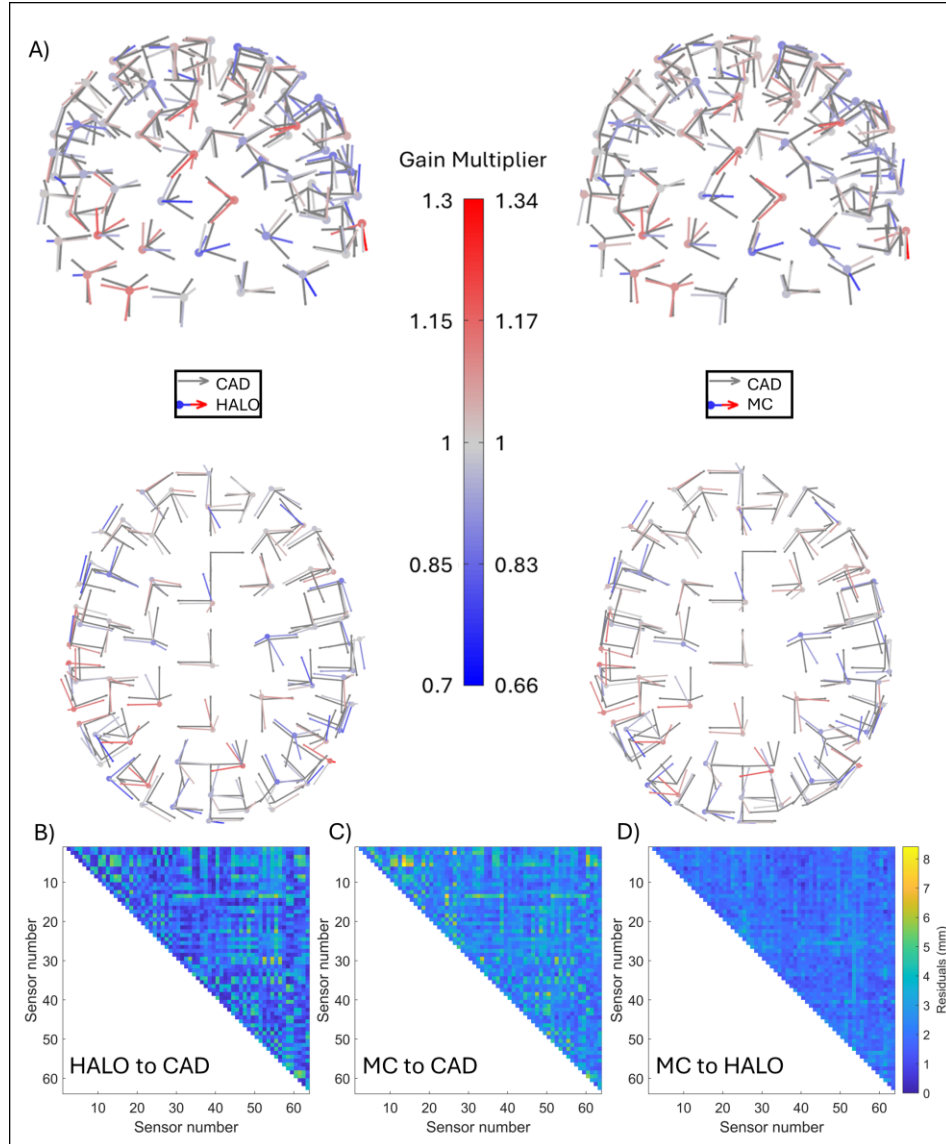


Figure 8.8: Quantifying the accuracy of calibration-derived sensor locations. *A)* CAD- (grey) and calibration- (coloured) derived sensor locations, orientations and gains. **Left panel** shows HALO, **right panel** shows MC. In both cases, the data points show the sensor location, the arrows show three sensitive orientations, and the colour shows the gain multiplier. (in the case of the CAD-derived values the gain multiplier is assumed to be 1). **B)** Matrix showing the mean residual sensor-to-sensor distance between CAD- and HALO-derived locations. **C)** Matrix showing the mean residual sensor-to-sensor distance between CAD- and MC-derived locations. **D)** Matrix showing the mean residual sensor-to-sensor distance between MC- and HALO-derived locations.

Figure 8.9 shows how our calibration-derived estimates of the sensitive orientations of the OPM differ from the CAD models (these differences are measured as angles, so an angle of 10° means the orientation of the sensitive axis in the OPM differs by 10° from the orientation of its outer casing). Figure 8.9a-c plot the MC-derived angular discrepancy against the HALO-derived angular discrepancy. Panels A, B, and C show the x, y, and z axes of each OPM, respectively. In all three cases, the data points show the mean angular

discrepancy, for a single OPM, calculated across experimental runs. The error bar shows the standard deviation across runs, meaning a small error bar denotes good consistency in the calibration-derived orientation across experiments. In all cases, the best fit line is shown in red and the line of equality in black. The fact that these lines fall very close to each other indicates good agreement between methods (i.e., the sensitive orientation derived using the HALO is similar to that derived using the MC).

To quantify the deviation of the angles from the expected value for each sensor axis we calculated the mean, standard deviation, minimum, and maximum angular discrepancies across all runs and channels. These were: x-axis: $17.1 \pm 8.6^\circ$ (max/min = $37.1/2.0^\circ$); y-axis: $5.4 \pm 2.3^\circ$ (max/min = $10.7/0.3^\circ$) and z-axis: $10.3 \pm 5.3^\circ$ (max/min = $23.1/0.8^\circ$) using the HALO and x-axis: $17.2 \pm 8.5^\circ$ (max/min = $36.0/2.4^\circ$), y-axis: $5.4 \pm 2.4^\circ$ (max/min = $11.3/0.2^\circ$) and z-axis: $10.5 \pm 5.4^\circ$ (max/min = $23.7/1.3^\circ$) using the MC. The x-axis has the largest error and widest range of values and y-channel the smallest error and narrowest range of values.

The average angles between the HALO and MC recovered orientations were: x-axis: $1.6 \pm 1.3^\circ$ (max/min = $7.6/0^\circ$); y-axis $1.0 \pm 0.6^\circ$ (max/min = $4.8/0^\circ$) and z-axis $1.0 \pm 0.6^\circ$ (max/min = $3.5/0^\circ$). The wide discrepancy across both sensors and channels with the CAD model is maintained across methods, highlighting the importance of calibration.

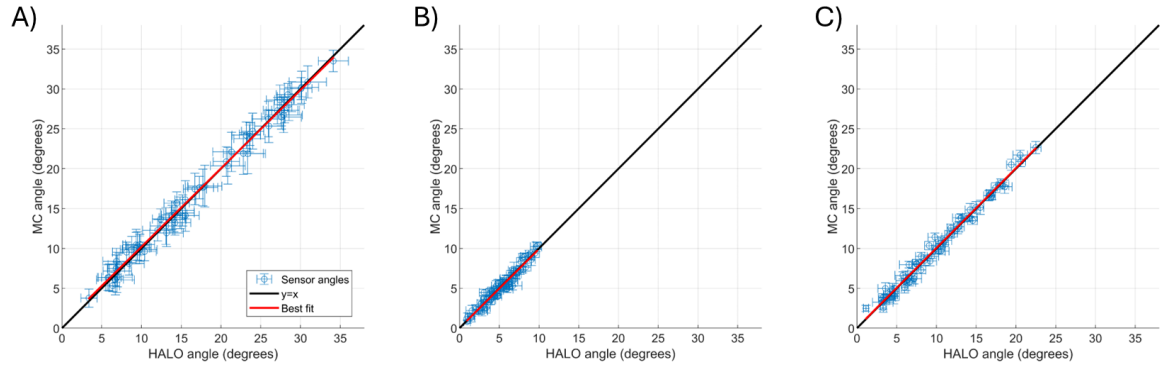


Figure 8.9: Estimating the accuracy of calibrated sensor orientations. All panels show the MC-derived angular discrepancy (with respect to CAD) against the HALO-derived angular discrepancy (also with respect to CAD). i.e. an angle of 10° would mean that the orientation of the sensitive axis in the OPM differs by 10° from the orientation of the outer casing of the sensor. Panels **A**, **B** and **C** show the x, y, and z axes of each OPM, respectively. Red lines show a best fit to the data. Black lines show the line of equality. All data points show the mean value across experimental runs and the error bars represent standard deviation. A close linear relationship suggests that the two calibration methods result in very similar sensitive orientations.

Figure 8.10 shows equivalent plots to Figure 8.9 but for the derived gain values. All values are centred around the expected 2.7 V/nT gain and again the

best-fit line closely follows the line of equality, showing that the two calibration techniques generate similar gain values, for each sensor. We again quantified the deviation of the gain from the expected value across each axis via computation of the mean, standard deviation, and minimum and maximum values across all runs and channels. These were: x-axis: 2.61 ± 0.24 V/nT (max/min = 3.15/2.01 V/nT), y-axis: 2.78 ± 0.19 V/nT (max/min = 3.75/2.39 V/nT) and z-axis: 2.67 ± 0.17 V/nT (max/min = 3.01/2.23 V/nT) for the HALO and x-axis: 2.63 ± 0.25 V/nT (max/min = 3.16/2.13 V/nT), y-axis: 2.80 ± 0.19 V/nT (max/min = 3.71/2.42 V/nT) and z-axis: 2.69 ± 0.16 V/nT (max/min = 3.07/2.29 V/nT) using the MC.

The average percentage deviation of the recovered gain values between the HALO and MC were: x-axis: $1.6 \pm 1.4\%$ (max/min 8.2/0.0%), y-axis $1.2 \pm 0.9\%$ (max/min 4.9/0.0%), z-axis $1.2 \pm 1.0\%$ (max/min 6.3/0.0%). Again, a discrepancy between the recovered values and the expected value and agreement across calibration techniques highlights the importance of calibration and the accuracy of both methods.

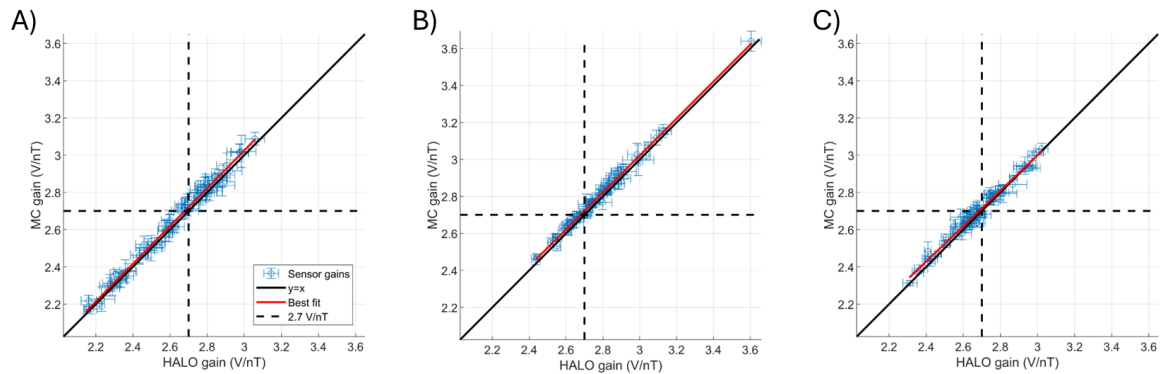


Figure 8.10: The accuracy of the calibrated sensor gains compared with the expected value (of 2.7 V/nT). Each panel plots the HALO-recovered gain against the MC-recovered gain. The values are shown as the mean across repeats, with the standard deviation shown by the error bars. Panels **A**), **B**) and **C**) show angles for the sensor X, Y and Z channels respectively. The dashed crosshairs show the expected gain value of 2.7 V/nT.

8.4.2 Human experiments

Figure 8.11 shows the beta band modulation induced by finger abduction. Figure 8.11A shows the group-averaged pseudo-T-statistical image, derived independently using the CAD- (top), HALO- (middle), and MC- (bottom) derived calibrations. The colour overlay, which shows the spatial signature of task induced beta power loss during movement, is thresholded to 80% of its minimum value. In all cases, the largest beta modulation is observed in the sensorimotor areas as would be expected. However, the pseudo-T value itself (a proxy metric for SNR) is ‘largest’ (i.e., average of most negative value of each

subject) for the HALO-derived calibration (-0.41 ± 0.03 – mean $\pm$ standard deviation over subjects); the MC-derived calibration resulted in a marginally lower pseudo-T value (-0.37 ± 0.03), and the CAD-derived calibration shows the smallest (least negative) value (-0.29 ± 0.04). This suggests a better reconstruction of the source for both the HALO and MC calibration, compared to the CAD model, with an average increase of 1.42 ± 0.09 and 1.31 ± 0.09 respectively.

Similarly, Figure 8.11A also shows the group-averaged TFS for a source at the location of the peak pseudo-T-statistic, for the three calibrations. The three plots are similar, with the expected movement-related beta decrease followed by an increase above baseline (the beta “rebound”) immediately following movement cessation. The TFSs reconstructed using either the HALO or MC calibrations show larger relative change from baseline compared to the TFS produced using CAD calibration. This difference is quantified in Figure 8.11B/C. Figure 8.11B shows the beta-band envelope averaged over participants, with the standard deviation indicated by the shaded area. Figure 8.11C shows the reconstructed source-space SNR for each subject. While both calibration methods show significant ($p = 0.0156$ for both methods, Wilcoxon sign-rank test) increases in SNR compared to the CAD-derived calibration, the HALO-derived calibration provides a greater increase. On average, the SNR increased by a factor of 2.85 ± 0.95 for the HALO and 1.77 ± 0.23 for the MC-derived calibration.

Figure 8.11D shows the location of maximum beta change for each subject, after transformation to the MNI-152 average brain. The average reconstructed location and its standard deviation in each axis are represented by the shaded ellipsoids. For all participants, the activity is localised to the precentral gyrus and the error ellipsoids overlap. However, for Subject 2 in the CAD-derived data, the peak location was found in the right precentral gyrus (i.e., an ipsilateral response) – the HALO- and MC-derived calibrations did not show this. The ellipsoids have volumes of 6417 mm^3 , 829 mm^3 , and 889 mm^3 for the CAD, HALO, and MC calibrations respectively, suggesting that the CAD-derived peak locations have a greater spatial spread while the HALO and MC are similar. These peak localisations are summarised in Table 8.1.

Figure 8.12 shows gamma band (40 – 60 Hz) oscillations induced by visual stimulation using the circular grating. (The Figure layout is equivalent to Figure 8.11.) The mean pseudo-T statistics at the locations of maximum gamma of each subject change were 0.48 ± 0.30 for the CAD calibration, 0.68 ± 0.47 for the HALO, and 0.62 ± 0.42 for the MC. Again, this suggests a better source reconstruction with the HALO and MC, with an average increase of 1.32 ± 0.17 and 1.22 ± 0.15 respectively. The TFS again show larger relative change when calibration is carried out using either the HALO or the MC compared to CAD. On average, the SNR increased by a factor of 1.32 ± 0.35 for the HALO and 1.25

± 0.41 for the MC-derived calibrations. However, whilst the improvement in SNR was significant for the HALO at the group level ($p = 0.047$ - Wilcoxon sign rank test) it was not significant for the MC ($p = 0.38$ - Wilcoxon sign rank test). Data in Figure 8C show that SNR improvements were less pronounced for gamma activity than they were for beta-band activity. Indeed, for some subjects SNR was marginally reduced – this will be addressed further in the Discussion. For all participants, using all three calibrations, the maximum gamma modulation activity was localised to primary visual cortex, as shown in Figure 8.12D. The ellipsoids have similar volumes of 822 mm^3 , 703 mm^3 , and 776 mm^3 for the CAD, HALO, and MC calibrations respectively.

Figure 8.13 shows the results of recording evoked responses to faces. Figure 8.13A shows the subject averaged (normalised) pseudo-Z-statistical map at a time $t = 108 \text{ ms}$, thresholded to 80% of its maximum value. All three cases show an average localisation in the occipital lobe. The activity derived using the CAD data localises entirely to the calcarine; for the MC-derived calibration, activity localises to the cuneus; and the HALO-derived activity bridges the two regions. Figure 8.13B shows the reconstructed timecourse for a point at the centre of mass of the calcarine as well as the left and right fusiform (as determined by the AAL atlas for each participant). For the three calibrations, occipital timecourses show similar temporal morphology, with the HALO- and MC-derived positions showing larger peaks at 80 ms and 108 ms compared to the CAD data. Figure 8.13C shows the occipital SNR for all participants, which increased significantly for both the HALO and MC compared to CAD ($p = 0.0156$ for both methods – Wilcoxon sign rank test). On average, the SNR increased by a factor of 1.31 ± 0.19 for the HALO and 1.21 ± 0.10 for the MC-derived calibrations. Figure 8.13D shows that, for all participants, the peak at 108 ms was localised to the occipital lobe with the mean location (i.e. the average across participants) remaining similar in each case. However, there was a greater standard deviation of peak location in the CAD-derived case. The ellipsoids have volumes of $13,363 \text{ mm}^3$, $3,808 \text{ mm}^3$, and $4,900 \text{ mm}^3$ for CAD, HALO, and MC calibrations respectively. This again implies a larger scatter of locations for the CAD-derived peak.

Method	Mean Position (mm)			Standard Deviation (mm)			Volume (mm^3)		
	Beta	Gamma	Evoked	Beta	Gamma	Evoked	Beta	Gamma	Evoked
CAD	[-26, -13, 64]	[-2, -92, 5]	[9, -91, 25]	[31, 8, 5]	[7, 4, 5]	[19, 10, 15]	6417	822	13363
HALO	[-40, -16, 60]	[-4, -93, 6]	[0, -91, 21]	[6, 7, 4]	[5, 5, 5]	[10, 5, 14]	829	703	3808
MC	[-39, -17, 63]	[-4, -92, 5]	[0, -91, 23]	[7, 7, 3]	[4, 5, 7]	[10, 7, 16]	889	776	4900

Table 8.1: Localisation summary – The mean and standard deviation for peak localisation across participants for each of the three tasks using each of the three calibration methods. The final column shows the volumes of the error ellipsoids plotted in Figures 8.11D, 8.12D, and 8.13D.

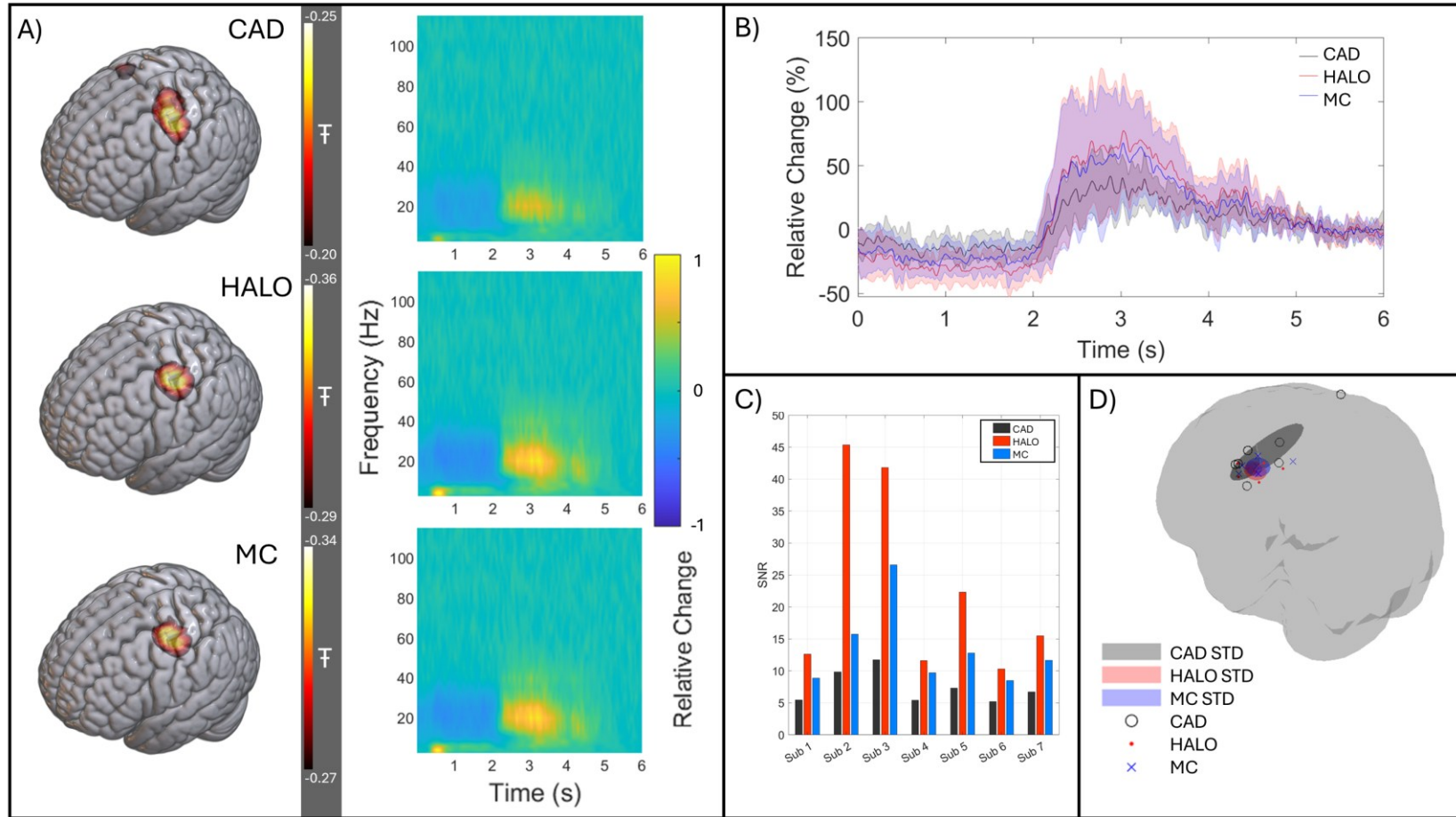


Figure 8.11: Beta band effects – **A)** Average pseudo-T-statistical image (thresholded at 80% of their minimum value) and a TFS showing the evolution of neural oscillatory activity at the location of peak beta modulation; data averaged across all participants for the CAD- (Top), HALO- (Middle), and MC- (Bottom) derived calibrations. **B)** The source reconstructed beta-band envelope for each method (CAD, HALO and MC in black, red and blue respectively) averaged across subjects with the standard deviation shown as a shaded area. This was again calculated at the location of largest beta modulation for each subject. **C)** Beta-band SNR calculated for each subject for CAD-, HALO-, and MC-derived calibration in black, red and blue respectively. **D)** The location of largest beta change for each participant, using all three calibration methods. CAD peaks are shown as black circles, HALO as red dots, and MC as blue crosses. In addition, the mean position and standard deviation in each axis are shown by shaded ellipsoids.

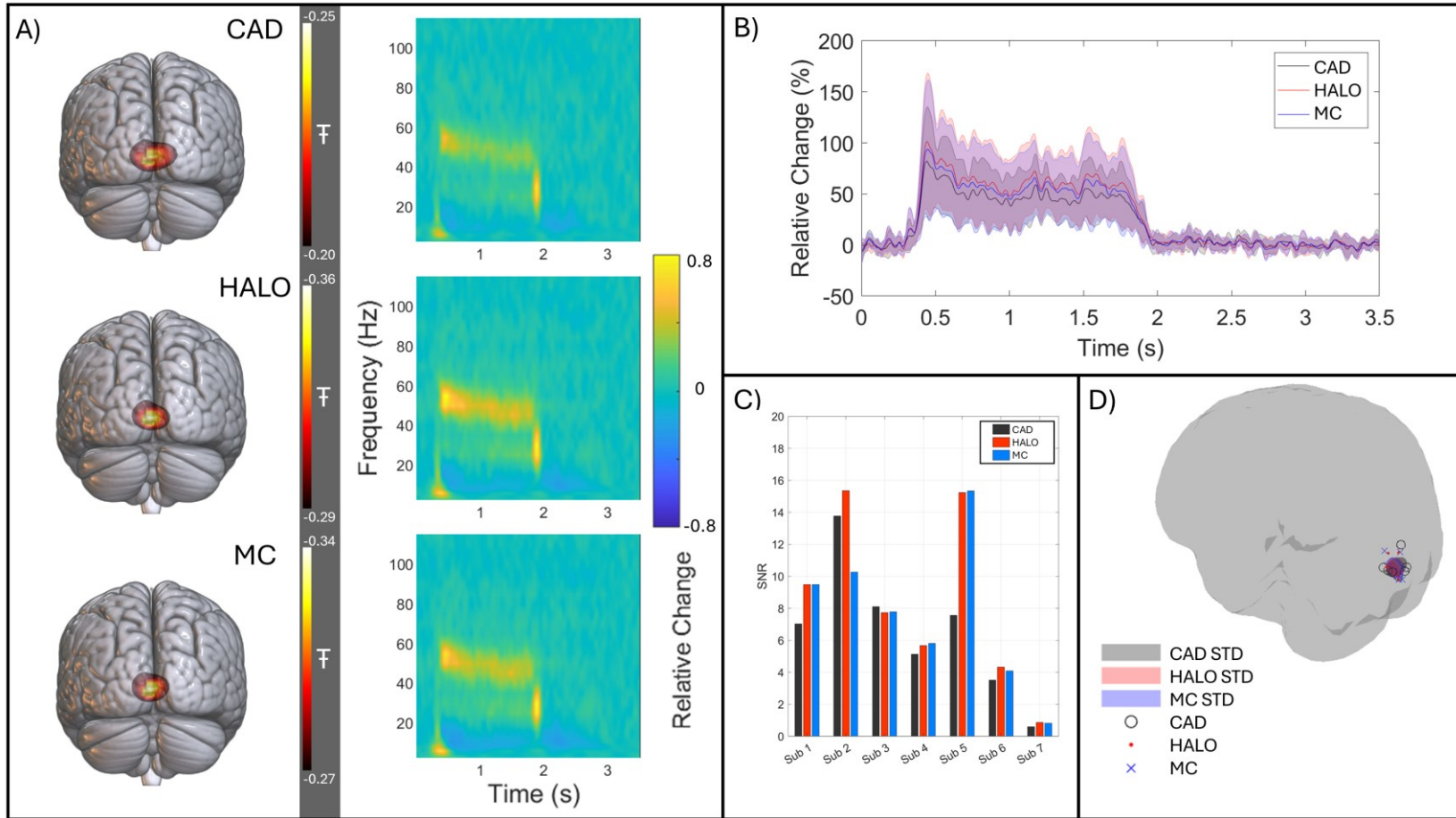


Figure 8.12: Gamma-band effects – **A)** Average pseudo-T-statistical images (thresholded at 80% of their maximum value) and a TFS showing the evolution of neural oscillatory activity at the location of peak gamma modulation; data averaged across participants for the CAD- (Top), HALO- (Middle), and MC- (Bottom) derived calibrations. **B)** The source reconstructed gamma-band envelope for each calibration method (CAD, HALO and MC in black, red and blue respectively) averaged across subjects with the standard deviation shown as a shaded area. This was again calculated at the location of largest gamma modulation for each subject. **C)** Gamma-band SNR calculated for each subject for CAD-, HALO-, and MC-derived calibration in black, red and blue respectively. **D)** The location of largest gamma change for each participant, using all three calibration methods. CAD peaks are shown as black circles, HALO as red dots, and MC as blue crosses. In addition, the mean position and standard deviation in each axis are shown by shaded ellipsoids.

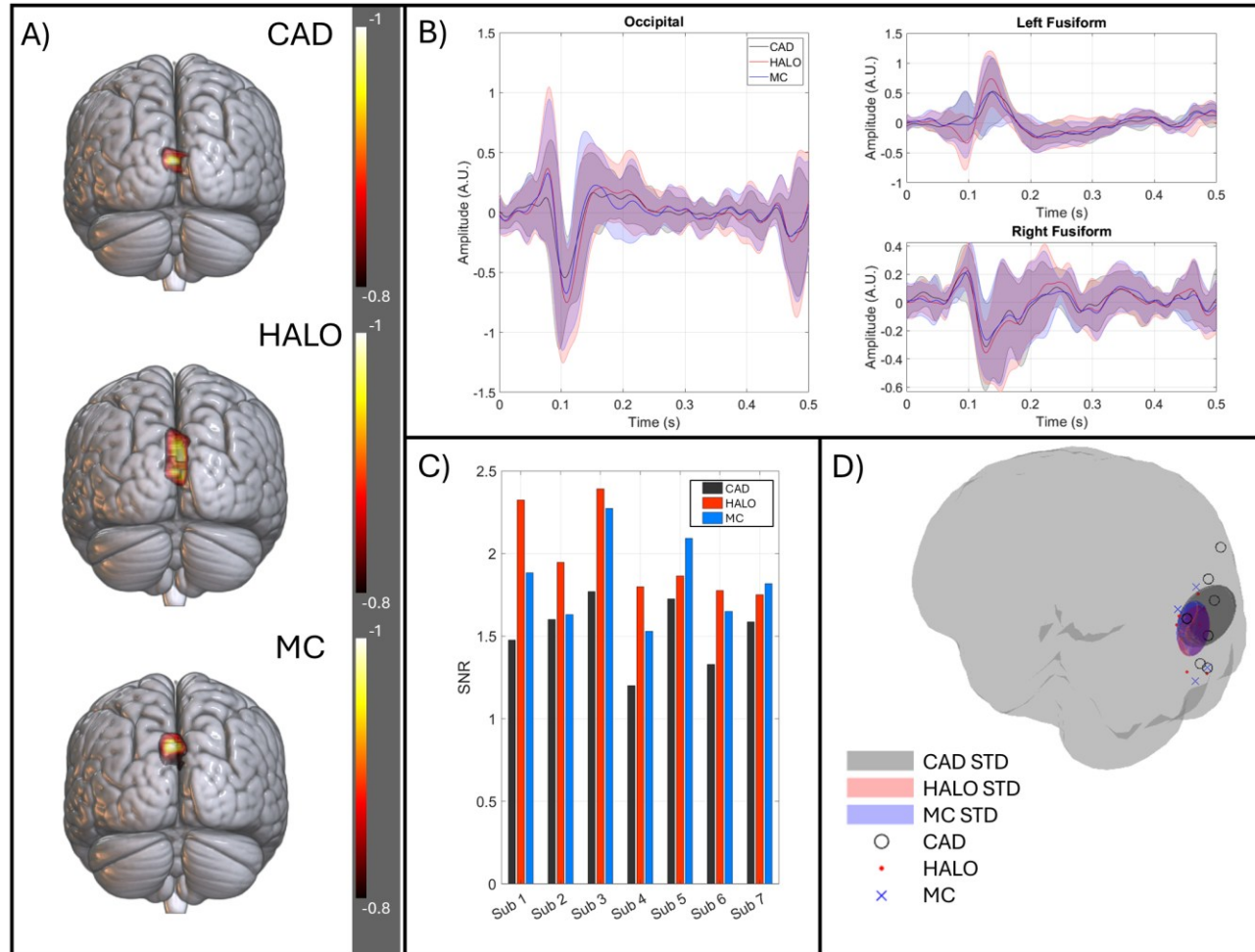


Figure 8.13: Evoked responses – **A)** Average pseudo-Z-statistical images (normalised by their maximum absolute value) taken at $t = 108$ ms and thresholded at 80% of the maximum. **B)** the source-reconstructed evoked response in the occipital, and left and right fusiform, shown for each calibration method (CAD, HALO and MC in black, red and blue respectively). All data are averaged across subjects with the standard deviation shown as a shaded area. The data were reconstructed for a point at the centre of mass of the calcarine, identified by the AAL atlas. **C)** SNR of the occipital response for each subject, evaluated for CAD-, HALO-, and MC-derived calibration (in black, red and blue respectively). **D)** The location of the largest change in evoked response at 108 ms; peaks for each participant are shown for the 3 calibration methods. CAD shown as black circles, HALO as red dots, and MC as blue crosses. In addition, the mean position and standard deviation in each axis are shown by shaded ellipsoids.

8.5 Discussion

MEG provides a sensitive means to characterise human brain function, and has significant clinical utility, for example to identify abnormal brain activity in epilepsy and determine its spatial origin (Rampp et al., 2019). However, the accuracy of MEG-derived metrics of both normal and abnormal brain function depends critically on knowing the relative locations of sensors, their sensitive axes, and their gain. If these key calibration parameters are incorrect, systematic errors in source localisation and reduced sensitivity necessarily follow. In this chapter, we demonstrate two independent techniques that use electromagnetic coils to produce known magnetic fields which can be used for OPM-MEG array calibration. We have shown that both techniques enable accurate determination of sensor location, orientation and gain; the two methods agree with each other (on average for position, orientation and gain by just 2.0 mm; 1.2° and 1.3% respectively), and both offer improvements in signal to noise ratio when characterising well-known neurophysiological processes in human MEG data.

The accuracy of calibration was assessed via measurement of the agreement between CAD-derived and calibration-derived sensor locations. This measurement was used because the CAD locations were the closest available metric to a “ground truth”. We assessed sensor-to-sensor distance for all sensor pairs, and the difference between CAD- and calibration-derived values was 2.08 ± 0.07 mm and 2.6 ± 0.2 mm for HALO and MC, respectively. This notionally offers a quantifiable “error” in the sensor localisation (and consequently calibration) process. However, it is likely that this scale of variation originates not only from errors due to the calibration but also from inaccuracies in the CAD model of the helmet. Indeed, the high similarity between Figure 8.8B and C shows that the sensor-to-sensor pairings in which the HALO calibration differed most from CAD, were the same pairings for which the MC calibration differed from CAD. Further, the discrepancy between our calibration techniques (i.e., the HALO-to-MC difference of 1.97 ± 0.16 mm) was less than the discrepancy between either technique and CAD. Errors in the CAD model likely come from multiple sources including inaccuracies in 3D printing, warping of the OPM helmet over time, and inaccuracies in sensor placement in the helmet. It is likely that these issues could explain a 2-mm discrepancy. Our localisation errors on the 2-mm scale agreed well with those reported by Iivanainen et al. (3.3 mm) using a similar methodology (Iivanainen et al., 2022). Both the existing CAD and the calibrated sensor locations agree with the minimum accuracy suggested by Zetter and colleagues (Zetter et al., 2018), of <4 mm, required to be comparable to existing cryogenic MEG systems.

Unlike the sensor locations, we have no ground truth metric of sensor orientation, save that the orientation depends on the direction of modulation fields made by on-board coils, which we assume to be parallel with the axes of

the outer casing of the sensor. We found that whilst the sensitive axes broadly pointed along the assumed direction, there were differences of $\sim 17^\circ$ for X-axes, $\sim 5^\circ$ for Y-axes and $\sim 10^\circ$ for Z-axes. In agreement with our sensor location results, these values were robust both across independent experiments using the same calibration procedure, and across our two (independent) calibration techniques (by 1.2° on average across all channels). It is noteworthy that Zetter et al. found that channel orientation should be known to a precision of $<10^\circ$ for MEG reconstruction; this would be met by most (but not all) channels using the CAD determined orientations but would be met (and bettered) in full following calibration.

For sensor gain we compared our results to the assumed values of 2.7 V/nT. There was again a significant spread in values, with a standard deviation in each axis between 6% and 10% of its mean. These differences from the assumption are large, and indeed (Nugent et al., 2022) indicated from simulation work that gain errors $>5\%$ can completely remove the capability of a dense scalp-mounted patch array of OPMs to resolve nearby sources. It is thus interesting that despite this significant spread of gain values our human data were not dramatically impacted when the assumed calibration was used. We suggest this is due to a larger spacing of sensors in our rigid helmets which hold sensors slightly away from the scalp surface compared to the simulation work. The system used here has been shown to offer similar performance to cryogenic devices (e.g., Rhodes et al., 2023; Safar et al., 2024; Tierney et al., 2020). We investigated the relationship between gain errors (up to 10%) and spatial discrimination of OPM-MEG systems for shallow and deep sources, finding noticeable differences only at high SNR (100 nAm sources). As the channel density of systems is increased to answer questions about the fundamental spatial resolution that is possible with OPM-MEG, calibration will clearly become a priority.

We also note that dynamic gain changes due to field variations (from environmental or significant movement artefacts, which are not present in our data here) would not be accounted for by our calibration method. If significant field changes were expected one could alleviate concerns with dynamic active shielding, performing calibration at regular intervals during an experiment, and by operating sensors in closed-loop mode.

In the human MEG experiments, all methods allowed sources to be localised to the expected cortical regions, demonstrating that even without calibration, MEG analysis was robust. However, several measurable improvements were afforded by performing the calibration. Firstly, the maximum pseudo-T-statistics increased, implying a better source reconstruction. Secondly, the spatial spread of peak locations (measured by the ellipsoid volumes) tended to be smaller following calibration (at least for beta and evoked responses). Perhaps most importantly, the SNR of all three measured MEG

responses was increased by calibration. The improvements in source space sensitivity and spatial precision result from the beamformer algorithm's exploitation of the improved match of the data to the MEG forward model after calibration. This may also explain why the improvement was larger for the beta band than it was for the gamma band. In the beta band, movement of a single digit likely evokes activity in a relatively small region of the motor cortex, and consequently the magnetic field generated looks dipolar in nature. In the gamma band, the visual stimulus was large and centrally presented, which likely evokes activity in both left and right hemispheres. This larger volume of activation is expected to generate a field that is less dipolar. If this departure from a dipole model is a larger source of error than that introduced by inaccurate calibration, then the improvement afforded by calibration would be relatively subtle. It is therefore possible (even likely) that calibration will not improve all MEG localisations.

Here, we showed that calibration improves beamformer localisation of induced and evoked effects. However, improvements should be maintained across other processing techniques. For example, the ability of the signal space separation method (SSS) (Taulu et al., 2005; Taulu and Kajola, 2005) and similar magnetic multipole modelling approaches (including homogeneous field correction (HFC) (Tierney et al., 2021) and adaptive multipole models (AMM (Tierney et al., 2024)) to reject interference should be improved by accurate calibration due to an increased capability to discriminate spatially the measurable field patterns across the helmet (Nurminen et al., 2008). It has been shown that multi-axis sensors, especially triaxial sensors as used in the current generation of OPM-MEG devices, offer distinct advantages when applying such models (Nurminen et al., 2013; Tierney et al., 2024, 2022) (compared to sensors which only measure a single component of field) as the angle between the subspace of harmonics which span the neuronal signals and interference is dramatically increased (from $\sim 10^\circ$ in a conventional MEG system (Taulu et al., 2005) to $\sim 60^\circ$ in the OPM-MEG system presented here (Holmes et al., 2023a)). However, temporal extensions to the purely spatial models (e.g., tSSS (Taulu and Simola, 2006)) have so far been required to fully separate brain signal from background fields, implying calibration errors hinder performance (Holmes et al., 2024; Tierney et al., 2024). Future work should look to verify this improvement.

Finally, in terms of practicality each calibration process (HALO and MC) took a similar time (c.1 min) to complete. Calibration could therefore easily be performed at the beginning of a scan with relatively little disruption to the participant or experimenters. However, the repeatability of results implies that calibration need not necessarily be performed prior to every experiment. Here we showed that calibrations were stable across multiple repeats in a single day, implying one calibration per day would be sufficient. Future work may offer further insight into stability over longer periods (e.g. could calibration be performed only once per week?). However, this would only be practical if OPMs

stayed in the same relative locations in a rigid helmet. In the case of a flexible (EEG-like) or adaptable OPM mounting, having a calibration procedure that can be applied every time the sensor array morphology is changed is critical. Related to this, the HALO has the advantage that it is attached to the helmet, and therefore calibration can be carried out even in the presence of large subject head movement. In contrast, the MC calibration accuracy would decrease with subject motion during the calibration. Whether such movement could be accounted for remains a topic for further study. According to the sensor localisation results, the HALO was marginally more accurate than the MC and this was generally reflected in the human MEG experiments. It is possible that the MC performed worse as the true variation of the field produced by each of the coils was not captured by the $40 \times 40 \times 40 \text{ cm}^3$ 10-cm resolution grid used to record the data for the MC forward model. (A finer spacing and wider volume could improve this). Furthermore, the MC are at least 1.4 m away from the sensors, meaning their spatial variation may be too slow by the time they reach the sensors to discriminate sensor locations. This said, it is noteworthy that, for the HALO, the accuracy of sensor locations drops with distance from the HALO (see appendix), perhaps as the field amplitude from the spiral coil becomes more dipolar with distance, deviating from the nearby moment (which was calibrated with a fluxgate sensor). It is also possible that some degrees of freedom in the magnetic field could be poorly sampled due to the shared orientation of each coil in the HALO. These issues could be addressed in several ways. For example, by mounting coils into the helmet itself (rather than on a plane riding above the helmet but maintaining the advantages of robust printing to get structure). For example, Adachi and colleagues embedded small coils into planar magnetoresistive sensor arrays developed for magnetocardiography (MCG) (Adachi et al., 2019). Coil current distributions could also be adapted taking the form of bi-planar field cancellation systems (e.g., Holmes et al., 2018; Zetter et al., 2020) to produce orthogonal fields from coils mounted on a planar PCB. Coils for calibration could also be worn by the participant, as demonstrated by Pfeiffer et al., 2020, 2018. Though we note that with such systems the proximity of the coils to the OPMs will generate focal field patterns across the sensor array. This will necessitate an improved starting guess for the optimisation algorithm than was needed in our case to avoid finding a solution in a local minimum. For our methods, the field patterns from each coil in the HALO and the MC vary similarly across the array, allowing simple navigation of the search space by the minimisation algorithm to reach the global minimum.

8.6 Conclusion

We have presented two methods to achieve complete OPM-MEG system calibration (measuring sensor location, orientation and gain). Both methods were based on accurately generating and modelling well-characterised magnetic fields over the sensor array. Our results show that these techniques offer an accurate means to calibrate an OPM array, and that the two methods agree strongly with each other (on average for position, orientation and gain by just 2.0 mm; 1.2°

and 1.3% respectively). Further, when applied to human MEG experiments, both methods offer significantly improved SNR compared to an assumed calibration. As OPM-MEG matures, arrays become denser, channel count increases, and the technology becomes more widely used for clinical applications, the importance of calibration to obtain reliable data will increase. Technologies for calibration will therefore likely become a core part of an OPM-MEG system.

Summary and outlook

As outlined in the introduction, the work presented in this thesis aimed to:

1. **Demonstrate OPM-MEG Sensitivity in Cognitive Neuroscience.**
2. **Advance OPM-MEG Technology through Improved Magnetic Shielding.**

The first objective was addressed in Chapter 6 by measuring subtle differences in beta band amplitude during a selective attention task. The results discussed in this chapter not only demonstrate the sensitivity, spatial resolution, and flexibility offered by OPM-MEG, but also show that such a system can already be employed to answer questions relevant to the field of neuroscience. The data were obtained to probe the underlying bursting dynamics that drive the modulation of beta band amplitude. As discussed in Section 6.5, the study does not come without limitations. Measuring such subtle effects can be difficult, especially since the OPM data can be affected by participant movements and drifts in the background field. Thankfully, the technique developed by Rea et al., 2021a, was employed to lower the background field to around ~ 0.3 nT, allowing for measurement of subtle beta modulation. This shows that OPM-MEG is not just an emerging experimental technology but has already become a practical tool for understanding brain dynamics. The ability to simply place the OPM helmet on the participants and start the data acquisition process right away without the need for extensive preparation makes it a “plug and play” system, allowing researchers from a range of different fields to carry out neuroscience research without technical knowledge about the system’s inner workings. This ease of use, combined with the high-quality neural data it provides, underscores the potential of OPM-MEG to become a standard technology in cognitive and clinical neuroscience research.

Chapters 7 and 8 address the second aim of the thesis. First, the work shown in Chapter 7 presents a novel active shielding system which builds and improves upon previous work on field cancellation for OPM-MEG. Prior to this thesis, Holmes et al., 2018a, had designed and constructed a set of biplanar coils to enable OPM-MEG. In line with the arguments presented in Chapter 3, the OPMs introduce a strict zero field requirement due to their dynamic range and susceptibility to movement artifacts. Active shielding has therefore been key in realising the potential of OPM-MEG. Although effective, the biplanar coil system introduced certain constraints. First, participants wearing the helmet cannot move beyond the target volume where the field is cancelled since it is fixed in space. Additionally, the intricate coil windings can be difficult to manufacture, with the final set of coils occupying a considerable space within the MSR. As demonstrated in Chapter 7, the newly developed matrix coil system solves these issues. The multi-coil solution can null the background field in many positions throughout the MSR, opening up the possibilities for novel

experimental paradigms. Also shown in Chapter 8, this approach can enable scanning of participants while standing and during ambulatory movement.

The improved version of the matrix coils shown in Chapter 8 poses a significant advancement for OPM-MEG. The small footprint of the coils placed around the walls, ceiling and floor of the MSR leaves the inner volume of the room free of obstructions, making it a lot easier to perform experiments involving participants movement, or experiments where an additional person is required to be in the room. Furthermore, this design enhances the overall ease of use of OPM-MEG by reducing constraints on participant positioning and motion, making it more suitable for studying naturalistic behaviours and real-world cognitive tasks. Additionally, the ability to more accurately calibrate the sensor orientation and gain further improves the overall quality of the MEG data. Results obtained with both the HALO and the matrix coils can help increase the signal-to-noise ratio of the measured brain signals and improve many of the signal processing steps used in every MEG study, such as noise removal and source localisation. In conclusion, the advancements discussed in this thesis not only refine the practical implementation of OPM-MEG but also broadens its potential applications, including clinical assessments, developmental studies, and even brain-computer interface research.

Future work

Having addressed how this thesis has helped both improve and demonstrate the capabilities of OPM-MEG, bringing it closer to realising its potential applications, we now discuss how some of the work presented could be expanded in the future to push this technology further.

Attentional modulation of the beta band

The work on beta modulation covered in Chapter 6 employed a time-delay embedded Hidden Markov Model (HMM) to study the underlying bursting dynamics. The results obtained helped probe the mechanisms driving the observed attentional modulation of the beta band, demonstrating that these modulations are underpinned by discrete, burst-like events rather than sustained oscillatory activity. However, while this analysis provided a window into the temporal characteristics of beta dynamics, further investigation is warranted. In particular, connectivity analysis—both static and dynamic—might help shed more light on the spatial organisation and inter-regional communication patterns that contribute to attentional modulation. Connectivity analysis could probe how regions linked to logical thinking, memory and decision making play a role in top-down inhibition. This could be performed using traditional connectivity measures such as Phase Difference Derivative (PDD), Amplitude Envelope

Correlation (AEC) or even connectivity measures obtained using HMMs (Seedat et al., 2020; Tewarie et al., 2019).

Beyond the study of connectivity, alternative data-driven models could be employed to study this phenomenon. The HMM we utilised assumes the possible states to be mutually exclusive, which might not fully capture the complexity of overlapping neural processes that often co-occur during cognitive tasks. This analysis could be performed using probabilistic models that permit partial state occupancy, such as the Dynamic Network Modes (DyNeMo) framework, developed by Gohil et al., 2022.

Lastly, this study could be expanded by obtaining additional datasets from paradigms designed to study selective attention during tasks requiring a different modality of sensory processing. For example, separate datasets could be obtained for paradigms involving analogous auditory or visual processing tasks. The resulting data could help study the role of higher-order brain regions in the observed attentional modulation.

Active shielding

The work on active background field cancellation discussed in both Chapters 7 and 8 has shown that multi-coil systems could be the way forward to realise the potential applications of OPM-MEG. Future work should aim to push the limits of the matrix coil system. Avenues of progress include improving calibration of the coils, real time dynamic nulling and nulling of larger volumes within the MSR. This would potentially allow participants to move more freely without the need for complex optical tracking systems, thereby expanding the range of possible experimental paradigms and improving participant comfort. Ongoing developments include efforts to perform hyperscanning with OPMs—simultaneously nulling the magnetic field in separate spatial volumes—using the latest matrix coil configuration.

Additional challenges must be addressed to realise the potential clinical use of OPM-MEG. In relation to magnetic shielding, key issues include improving ease of use for non-specialist operators, reducing the overall cost and complexity of the system, and ensuring reliable operation in high-interference urban environments—particularly relevant as many clinical facilities are located in densely populated areas with substantial ambient magnetic noise. System cost could be greatly reduced by constructing MSRs that require fewer shielding layers, which would not only reduce the overall costs but also weight. This would require improved active shielding, capable of cancelling fields of much larger amplitudes (hundreds of nT). Work is already underway to study the feasibility of such a system, with some early results suggesting that this might be possible

through a combination of active shielding and noise removal techniques, such as signal space separation (Holmes et al., 2023a).

Sensor calibration and localisation

Modern epilepsy treatments, where presurgical mapping is required, already rely on the use of MEG to localise the seizure onset zone. This requires high precision spatial mapping of MEG signals, which emphasises the need for accurate sensor calibration and co-registration; without such calibration, localisation can become inaccurate. The results shown in Chapter 8 are therefore of importance.

The methods developed in Chapter 8 could be further expanded by developing additional ways to more precisely compare the calibration methods. As covered in the discussion, both calibration methods were compared against the assumed CAD file sensor locations and orientations, these may not accurately reflect the actual placement of the sensor array. As outlined, tolerances in the 3D printing process and slight sensor displacements in the helmet slots likely affected the scale of the measured errors.

Future research could aim to further disentangle the sources of these errors. Specifically, differentiating the proportion of error introduced by inherent manufacturing variability in the sensors themselves from that introduced by imperfect sensor positioning within the helmet. This could involve controlled experiments using precision phantoms or improved mechanical alignment strategies. Results could help inform design decisions of the sensors themselves to improve orthogonalization or maybe alter the helmet design. Additionally, developing independent, ground-truth validation methods—such as optical tracking or 3D scanning of the assembled helmet—could provide more accurate reference data for assessing calibration accuracy.

Lastly, although at a higher cost than the HALO, the matrix coils may offer more versatility for future system improvements. With an accurate enough forward model, one could not only find the relative positions of the sensors, but localise the helmet within the MSR, and subsequently cancel the field in the surrounding volume. Furthermore, future work to make the calibration procedures faster and easier to use for scanner operators is already being undertaken. As discussed in Chapter 8, a faster calibration procedure could potentially be used at different intervals throughout a scan, ensuring that sensor locations and orientations remain accurate even in the presence of gradual shifts due to head movement or thermal drift. This would help maintain spatial fidelity across longer recordings and improve the robustness of source localisation,

especially in paradigms involving naturalistic behaviour or extended scanning sessions.

Final Remarks

In summary, this thesis has demonstrated both the scientific utility and technological readiness of OPM-MEG. By applying this emerging modality to uncover the fine-grained dynamics of attentional modulation, and by developing robust, scalable solutions for magnetic field control, it has contributed meaningfully to the advancement of both methodology and application. The work presented here contributes to bridging the gap between proof-of-concept and practical deployment, showing that OPM-MEG is no longer just a promising idea, but a viable platform for real-world neuroscience. As the technology continues to evolve, it is poised not only to complement existing neuroimaging tools—but to redefine the boundaries of what brain research can achieve.

Appendix I: Array formation variations

As explained in the methods section of Chapter 6, the number of sensors varied for different subjects. To assess the potential impact of this, we performed an investigation into the brain coverage provided by both arrays. Using a forward solution based on the dipole and single shell models, we computed the Frobenius norm of the forward fields generated by all AAL derived source positions. These values were derived for all subjects (using the sensor locations/orientations that were determined in the experimental sessions). For each subject these values were normalised by their maximum value (across all AAL regions), averaged over subjects scanned with different sensor counts, and plotted for all brain regions. Results are shown in Figure A1. Differences in coverage were found to be minimal in regions of interest to this study (i.e. sensorimotor cortices). This allows us to derive results from these regions without introducing biases in source space outcomes resulting from coverage variations.

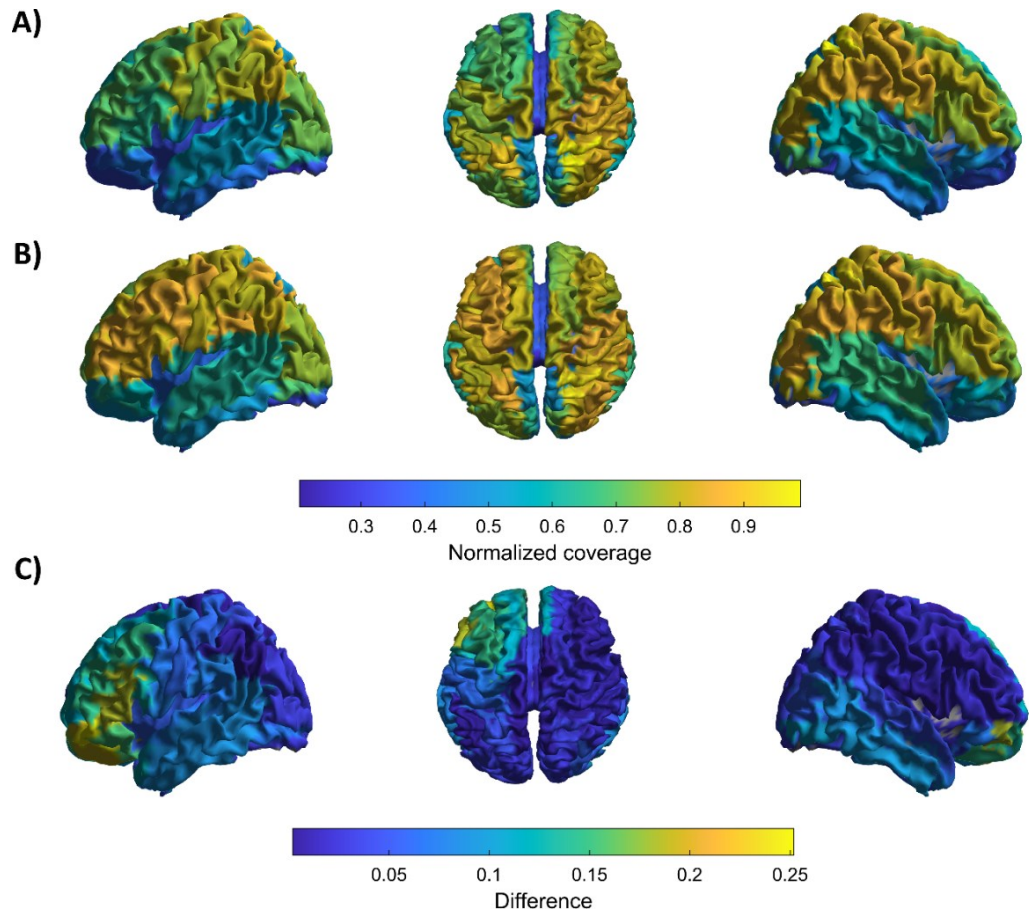


Figure A1: Sensor brain coverage. Brain surface colourmaps representing the normalized Frobenius norm of the AAL atlas regions for scans with **A)** 132 channels, **B)** 192 triaxial sensors. **C)** shows the difference between the two channel counts.

Bibliography

- Abbott, J.J., 2015. Parametric design of tri-axial nested Helmholtz coils. *Review of Scientific Instruments* 86, 054701. <https://doi.org/10.1063/1.4919400>
- Adachi, Y., Oyama, D., Higuchi, M., Uehara, G., 2023. A Spherical Coil Array for the Calibration of Whole-Head Magnetoencephalograph Systems. *IEEE Transactions on Instrumentation and Measurement* 72, 1–10. <https://doi.org/10.1109/TIM.2023.3265750>
- Adachi, Y., Oyama, D., Terazono, Y., Hayashi, T., Shibuya, T., Kawabata, S., 2019. Calibration of Room Temperature Magnetic Sensor Array for Biomagnetic Measurement. *IEEE Transactions on Magnetics* 55, 1–6. <https://doi.org/10.1109/TMAG.2019.2895355>
- Afach, S., Bison, G., Bodek, K., Burri, F., Chowdhuri, Z., Daum, M., Fertl, M., Franke, B., Grujic, Z., Hélaine, V., Henneck, R., Kasprzak, M., Kirch, K., Koch, H.-C., Kozela, A., Krempel, J., Lauss, B., Lefort, T., Lemièrre, Y., Meier, M., Naviliat-Cuncic, O., Piegsa, F.M., Pignol, G., Plonka-Spehr, C., Prashanth, P.N., Quémener, G., Rebreyend, D., Rocchia, S., Schmidt-Wellenburg, P., Schnabel, A., Severijns, N., Voigt, J., Weis, A., Wyszynski, G., Zejma, J., Zenner, J., Zsigmond, G., 2014. Dynamic stabilization of the magnetic field surrounding the neutron electric dipole moment spectrometer at the Paul Scherrer Institute. *Journal of Applied Physics* 116, 084510. <https://doi.org/10.1063/1.4894158>
- Alem, O., Hughes, K.J., Buard, I., Cheung, T.P., Maydew, T., Griesshammer, A., Holloway, K., Park, A., Lechuga, V., Coolidge, C., Gerginov, M., Quigg, E., Seames, A., Kronberg, E., Teale, P., Knappe, S., 2023. An integrated full-head OPM-MEG system based on 128 zero-field sensors. *Front. Neurosci.* 17. <https://doi.org/10.3389/fnins.2023.1190310>
- Allen, C.M., Halsey, L., Topcu, G., Rier, L., Gascoyne, L.E., Scadding, J.W., Furlong, P.L., Dunkley, B.T., das Nair, R., Brookes, M.J., Evangelou, N., 2021. Magnetoencephalography abnormalities in adult mild traumatic brain injury: A systematic review. *Neuroimage Clin* 31, 102697. <https://doi.org/10.1016/j.nicl.2021.102697>
- Allred, J.C., Lyman, R.N., Kornack, T.W., Romalis, M.V., 2002. High-Sensitivity Atomic Magnetometer Unaffected by Spin-Exchange Relaxation. *Phys. Rev. Lett.* 89, 130801. <https://doi.org/10.1103/PhysRevLett.89.130801>
- Altarev, I., Fierlinger, P., Lins, T., Marino, M.G., Nießen, B., Petzoldt, G., Reisner, M., Stüiber, S., Sturm, M., Taggart Singh, J., Taubenheim, B., Rohrer, H.K., Schläpfer, U., 2015. Minimizing magnetic fields for precision experiments. *Journal of Applied Physics* 117, 233903. <https://doi.org/10.1063/1.4922671>

- Andersen, L.M., Oostenveld, R., Pfeiffer, C., Ruffieux, S., Jousmäki, V., Hämäläinen, M., Schneiderman, J.F., Lundqvist, D., 2017. Similarities and differences between on-scalp and conventional in-helmet magnetoencephalography recordings. *PLOS ONE* 12, e0178602. <https://doi.org/10.1371/journal.pone.0178602>
- Åström, K.J., Hägglund, T., 1995. PID Controllers: Theory, Design, and Tuning. ISA - The Instrumentation, Systems and Automation Society, Research Triangle Park, North Carolina.
- Auzinsh, M., Budker, D., Kimball, D.F., Rochester, S.M., Stalnaker, J.E., Sushkov, A.O., Yashchuk, V.V., 2004. Can a Quantum Nondemolition Measurement Improve the Sensitivity of an Atomic Magnetometer? *Phys. Rev. Lett.* 93, 173002. <https://doi.org/10.1103/PhysRevLett.93.173002>
- Auzinsh, M., Budker, D., Rochester, S., Auzinsh, M., Budker, D., Rochester, S., 2010. Optically Polarized Atoms: Understanding light-atom interactions. Oxford University Press, Oxford, New York.
- Bagic, A.I., Knowlton, R.C., Rose, D.F., Ebersole, J.S., Committee, for the A.C.P.G. (CPG), 2011. American Clinical Magnetoencephalography Society Clinical Practice Guideline 1: Recording and Analysis of Spontaneous Cerebral Activity*. *Journal of Clinical Neurophysiology* 28, 348. <https://doi.org/10.1097/WNP.0b013e3182272fed>
- Baillet, S., 2017. Magnetoencephalography for brain electrophysiology and imaging. *Nat Neurosci* 20, 327–339. <https://doi.org/10.1038/nn.4504>
- Baker, A.P., Brookes, M.J., Rezek, I.A., Smith, S.M., Behrens, T., Probert Smith, P.J., Woolrich, M., 2014. Fast transient networks in spontaneous human brain activity. *eLife* 3, e01867. <https://doi.org/10.7554/eLife.01867>
- Bardeen, J., Cooper, L.N., Schrieffer, J.R., 1957. Theory of Superconductivity. *Phys. Rev.* 108, 1175–1204. <https://doi.org/10.1103/PhysRev.108.1175>
- Barone, J., Rossiter, H.E., 2021. Understanding the Role of Sensorimotor Beta Oscillations. *Frontiers in Systems Neuroscience* 15. <https://doi.org/10.3389/fnsys.2021.655886>
- Barratt, E.L., Tewarie, P.K., Clarke, M.A., Hall, E.L., Gowland, P.A., Morris, P.G., Francis, S.T., Evangelou, N., Brookes, M.J., 2017. Abnormal task driven neural oscillations in multiple sclerosis: A visuomotor MEG study. *Hum Brain Mapp* 38, 2441–2453. <https://doi.org/10.1002/hbm.23531>
- Bastos, A.M., Schoffelen, J.-M., 2015. A Tutorial Review of Functional Connectivity Analysis Methods and Their Interpretational Pitfalls. *Front Syst Neurosci* 9, 175. <https://doi.org/10.3389/fnsys.2015.00175>

- Bauer, M., Stenner, M.-P., Friston, K.J., Dolan, R.J., 2014. Attentional Modulation of Alpha/Beta and Gamma Oscillations Reflect Functionally Distinct Processes. *Journal of Neuroscience* 34, 16117–16125. <https://doi.org/10.1523/JNEUROSCI.3474-13.2014>
- Beato, F., Belorizky, E., Labyt, E., Le Prado, M., Palacios-Laloy, A., 2018. Theory of a Helium-4 parametric-resonance magnetometer based on atomic alignment. *Phys. Rev. A* 98, 053431. <https://doi.org/10.1103/PhysRevA.98.053431>
- Bell, W.E., Bloom, A.L., 1961. Optically Driven Spin Precession. *Phys. Rev. Lett.* 6, 280–281. <https://doi.org/10.1103/PhysRevLett.6.280>
- Bell, W.E., Bloom, A.L., 1957. Optical Detection of Magnetic Resonance in Alkali Metal Vapor. *Phys. Rev.* 107, 1559–1565. <https://doi.org/10.1103/PhysRev.107.1559>
- Bentin, S., Allison, T., Puce, A., Perez, E., McCarthy, G., 1996. Electrophysiological Studies of Face Perception in Humans. *Journal of Cognitive Neuroscience* 8, 551–565. <https://doi.org/10.1162/jocn.1996.8.6.551>
- Berger, H., 1933. Über das Elektrenkephalogramm des Menschen. *Archiv f. Psychiatrie* 100, 301–320. <https://doi.org/10.1007/BF01814740>
- Berger, H., 1929. Über das Elektrenkephalogramm des Menschen. *Archiv f. Psychiatrie* 87, 527–570. <https://doi.org/10.1007/BF01797193>
- Bernardi, G., Betta, M., Ricciardi, E., Pietrini, P., Tononi, G., Siclari, F., 2019. Regional Delta Waves In Human Rapid Eye Movement Sleep. *J. Neurosci.* 39, 2686–2697. <https://doi.org/10.1523/JNEUROSCI.2298-18.2019>
- Bloom, A.L., 1962. Principles of Operation of the Rubidium Vapor Magnetometer. *Appl. Opt., AO* 1, 61–68. <https://doi.org/10.1364/AO.1.000061>
- Borna, A., Carter, T.R., Colombo, A.P., Jau, Y.Y., McKay, J., Weisend, M., Taulu, S., Stephen, J.M., Schwindt, P.D.D., 2020a. Non-invasive functional-brain-imaging with an OPM-based magnetoencephalography system. *PLoS ONE* 15, 1–24. <https://doi.org/10.1371/journal.pone.0227684>
- Borna, A., Carter, T.R., Colombo, A.P., Jau, Y.-Y., McKay, J., Weisend, M., Taulu, S., Stephen, J.M., Schwindt, P.D.D., 2020b. Non-Invasive Functional-Brain-Imaging with an OPM-based Magnetoencephalography System. *PLOS ONE* 15, e0227684. <https://doi.org/10.1371/journal.pone.0227684>

- Borna, A., Carter, T.R., Goldberg, J.D., Colombo, A.P., Jau, Y.-Y., Berry, C., McKay, J., Stephen, J., Weisend, M., Schwindt, P.D.D., 2017. A 20-channel magnetoencephalography system based on optically pumped magnetometers. *Phys. Med. Biol.* 62, 8909. <https://doi.org/10.1088/1361-6560/aa93d1>
- Borna, A., Iivanainen, J., Carter, T.R., McKay, J., Taulu, S., Stephen, J., Schwindt, P.D.D., 2022. Cross-Axis projection error in optically pumped magnetometers and its implication for magnetoencephalography systems. *NeuroImage* 247, 118818. <https://doi.org/10.1016/j.neuroimage.2021.118818>
- Boto, E., Bowtell, R., Kruger, P., Fromhold, T., Morris, P., Meyer, S., Barnes, G., Brookes, M., 2016. On the Potential of a New Generation of Magnetometers for MEG: A Beamformer Simulation Study. *PLOS ONE* 11. <https://doi.org/10.1371/journal.pone.0157655>
- Boto, E., Holmes, N., Leggett, J., Roberts, G., Shah, V., Meyer, S.S., Muñoz, L.D., Mullinger, K.J., Tierney, T.M., Bestmann, S., Barnes, G.R., Bowtell, R., Brookes, M.J., 2018. Moving magnetoencephalography towards real-world applications with a wearable system. *Nature* 555, 657–661. <https://doi.org/10.1038/nature26147>
- Boto, E., Meyer, S.S., Shah, V., Alem, O., Knappe, S.A., Kruger, P., Fromhold, M., Morris, P.G., Bowtell, R.W., Barnes, G.R., Brookes, M.J., Lim, M., 2017. A New Generation of Magnetoencephalography: Room Temperature Measurements using Optically-Pumped Magnetometers. *NIST*.
- Boto, E., Seedat, Z.A., Holmes, N., Leggett, J., Hill, R.M., Roberts, G., Shah, V., Fromhold, T.M., Mullinger, K.J., Tierney, T.M., Barnes, G.R., Bowtell, R., Brookes, M.J., 2019. Wearable neuroimaging: Combining and contrasting magnetoencephalography and electroencephalography. *Neuroimage* 201, 116099. <https://doi.org/10.1016/j.neuroimage.2019.116099>
- Boto, E., Shah, V., Hill, R.M., Rhodes, N., Osborne, J., Doyle, C., Holmes, N., Rea, M., Leggett, J., Bowtell, R., Brookes, M.J., 2022. Triaxial detection of the neuromagnetic field using optically-pumped magnetometry: feasibility and application in children. *Neuroimage* 252, 119027. <https://doi.org/10.1016/j.neuroimage.2022.119027>
- Bowtell, R., Robyr, P., 1998. Multilayer Gradient Coil Design. *Journal of Magnetic Resonance* 131, 286–294. <https://doi.org/10.1006/jmre.1998.1369>
- Brantley, J.A., Luu, T.P., Nakagome, S., Zhu, F., Contreras-Vidal, J.L., 2018. Full body mobile brain-body imaging data during unconstrained

- locomotion on stairs, ramps, and level ground. *Sci Data* 5, 180133. <https://doi.org/10.1038/sdata.2018.133>
- Brookes, M.J., Boto, E., Rea, M., Shah, V., Osborne, J., Holmes, N., Hill, R.M., Leggett, J., Rhodes, N., Bowtell, R., 2021. Theoretical advantages of a triaxial optically pumped magnetometer magnetoencephalography system. *Neuroimage* 236, 118025. <https://doi.org/10.1016/j.neuroimage.2021.118025>
- Brookes, M.J., Hale, J.R., Zumer, J.M., Stevenson, C.M., Francis, S.T., Barnes, G.R., Owen, J.P., Morris, P.G., Nagarajan, S.S., 2011. Measuring functional connectivity using MEG: methodology and comparison with fcMRI. *Neuroimage* 56, 1082–1104. <https://doi.org/10.1016/j.neuroimage.2011.02.054>
- Brookes, M.J., Vrba, J., Robinson, S.E., Stevenson, C.M., Peters, A.M., Barnes, G.R., Hillebrand, A., Morris, P.G., 2008. Optimising experimental design for MEG beamformer imaging. *NeuroImage* 39, 1788–1802. <https://doi.org/10.1016/j.neuroimage.2007.09.050>
- Brookes, M.J., Woolrich, M.W., Barnes, G.R., 2012. Measuring functional connectivity in MEG: A multivariate approach insensitive to linear source leakage. *Neuroimage* 63, 910–920. <https://doi.org/10.1016/j.neuroimage.2012.03.048>
- Budker, D., Kimball, D.F.J., 2013. *Optical Magnetometry*. Cambridge University Press.
- Bullock, T.H., 1997. Signals and signs in the nervous system: The dynamic anatomy of electrical activity is probably information-rich. *Proc Natl Acad Sci U S A* 94, 1–6.
- Buzsáki, G., Anastassiou, C.A., Koch, C., 2012. The origin of extracellular fields and currents — EEG, ECoG, LFP and spikes. *Nat Rev Neurosci* 13, 407–420. <https://doi.org/10.1038/nrn3241>
- Carlson, J.W., Derby, K.A., Hawryszko, K.C., Weideman, M., 1992. Design and evaluation of shielded gradient coils. *Magnetic Resonance in Medicine* 26, 191–206. <https://doi.org/10.1002/mrm.1910260202>
- Celozzi, S., Araneo, R., Lovat, G., 2008. *Electromagnetic Shielding*. Wiley.
- Chapman, R.M., Ilmoniemi, R.J., Barbanera, S., Romani, G.L., 1984. Selective localization of alpha brain activity with neuromagnetic measurements. *Electroencephalography and Clinical Neurophysiology* 58, 569–572. [https://doi.org/10.1016/0013-4694\(84\)90047-6](https://doi.org/10.1016/0013-4694(84)90047-6)
- Chella, F., Zappasodi, F., Marzetti, L., Penna, S.D., Pizzella, V., 2012. Calibration of a multichannel MEG system based on the Signal Space

- Separation method. *Phys. Med. Biol.* 57, 4855.
<https://doi.org/10.1088/0031-9155/57/15/4855>
- Chesca, B., Kleiner, R., Koelle, D., 2004. SQUID Theory, in: *The SQUID Handbook*. John Wiley & Sons, Ltd, pp. 29–92.
<https://doi.org/10.1002/3527603646.ch2>
- Cignoni, P., Callieri, M., Corsini, M., Dellepiane, M., Ganovelli, F., Ranzuglia, G., 2008. MeshLab: an Open-Source Mesh Processing Tool. *The Eurographics Association*.
<https://doi.org/10.2312/LocalChapterEvents/ItalChap/ItalianChapConf2008/129-136>
- Clarke, J., 1994. SQUIDS. *Scientific American* 271, 46–53.
- Cohen, D., 1972. Magnetoencephalography: Detection of the Brain's Electrical Activity with a Superconducting Magnetometer. *Science* 175, 664–666.
<https://doi.org/10.1126/science.175.4022.664>
- Cohen-Tannoudji, C., Dupont-Roc, J., Haroche, S., Laloë, F., 1970. Diverses résonances de croisement de niveaux sur des atomes pompés optiquement en champ nul. I. Théorie. *Rev. Phys. Appl. (Paris)* 5, 95–101. <https://doi.org/10.1051/rphysap:019700050109500>
- Colclough, G.L., Brookes, M.J., Smith, S.M., Woolrich, M.W., 2015. A symmetric multivariate leakage correction for MEG connectomes. *NeuroImage* 117, 439–448.
<https://doi.org/10.1016/j.neuroimage.2015.03.071>
- Colombo, A.P., Carter, T.R., Borna, A., Jau, Y.-Y., Johnson, C.N., Dagel, A.L., Schwindt, P.D.D., 2016. Four-channel optically pumped atomic magnetometer for magnetoencephalography. *Opt Express* 24, 15403–15416. <https://doi.org/10.1364/OE.24.015403>
- Corsini, E., Acosta, V., Baddour, N., Higbie, J., Lester, B., Licht, P., Patton, B., Prouty, M., Budker, D., 2011. Search for plant biomagnetism with a sensitive atomic magnetometer. *Journal of Applied Physics* 109, 074701.
<https://doi.org/10.1063/1.3560920>
- Corvilain, P., Wens, V., Bourguignon, M., Capparini, C., Fourdin, L., Ferez, M., Feys, O., Tiège, X.D., Bertels, J., 2023. Extending the applicability of optically pumped magnetoencephalography toward early human life.
<https://doi.org/10.1101/2023.10.28.564455>
- Cubero, D., Marmugi, L., Renzoni, F., 2020. Exploring the limits of magnetic field focusing: Simple planar geometries. *Results in Physics* 19, 103562.
<https://doi.org/10.1016/j.rinp.2020.103562>
- Curio, G., Mackert, B.-M., Burghoff, M., Koetitz, R., Abraham-Fuchs, K., Härer, W., 1994. Localization of evoked neuromagnetic 600 Hz activity

- in the cerebral somatosensory system. *Electroencephalography and Clinical Neurophysiology* 91, 483–487. [https://doi.org/10.1016/0013-4694\(94\)90169-4](https://doi.org/10.1016/0013-4694(94)90169-4)
- da Silva Castanheira, J., Orozco Perez, H.D., Misic, B., Baillet, S., 2021. Brief segments of neurophysiological activity enable individual differentiation. *Nat Commun* 12, 5713. <https://doi.org/10.1038/s41467-021-25895-8>
- Dale, M.W., Morley, G.W., 2017. Medical applications of diamond magnetometry: commercial viability. <https://doi.org/10.48550/arXiv.1705.01994>
- Dang, H.B., Maloof, A.C., Romalis, M.V., 2010. Ultrahigh sensitivity magnetic field and magnetization measurements with an atomic magnetometer. *Applied Physics Letters* 97, 151110. <https://doi.org/10.1063/1.3491215>
- Dawson, G.D., 1947. CEREBRAL RESPONSES TO ELECTRICAL STIMULATION OF PERIPHERAL NERVE IN MAN. *J Neurol Neurosurg Psychiatry* 10, 134–140. <https://doi.org/10.1136/jnnp.10.3.134>
- de Pasquale, F., Della Penna, S., Snyder, A.Z., Lewis, C., Mantini, D., Marzetti, L., Belardinelli, P., Ciancetta, L., Pizzella, V., Romani, G.L., Corbetta, M., 2010. Temporal dynamics of spontaneous MEG activity in brain networks. *Proc Natl Acad Sci U S A* 107, 6040–6045. <https://doi.org/10.1073/pnas.0913863107>
- Dehmelt, H.G., 1958. Spin Resonance of Free Electrons Polarized by Exchange Collisions. *Phys. Rev.* 109, 381–385. <https://doi.org/10.1103/PhysRev.109.381>
- Den Otter, A.R., Geurts, A.C.H., de Haart, M., Mulder, T., Duysens, J., 2005. Step characteristics during obstacle avoidance in hemiplegic stroke. *Exp Brain Res* 161, 180–192. <https://doi.org/10.1007/s00221-004-2057-0>
- Dhungel, O., Mrózek, M., Lenz, T., Ivády, V., Gali, A., Wickenbrock, A., Budker, D., Gawlik, W., Wojciechowski, A.M., 2024. Near-zero-field microwave-free magnetometry with nitrogen-vacancy centers in nanodiamonds. <https://doi.org/10.48550/arXiv.2401.08246>
- Diesburg, D.A., Greenlee, J.D., Wessel, J.R., 2021. Cortico-subcortical β burst dynamics underlying movement cancellation in humans. *Elife* 10, e70270. <https://doi.org/10.7554/eLife.70270>
- Dong, H.F., Fang, J.C., Zhou, B.Q., Tang, X.B., Qin, J., 2012. Three-dimensional atomic magnetometry. *Eur. Phys. J. Appl. Phys.* 57, 21004. <https://doi.org/10.1051/epjap/2011110392>

- Eccles, J.C., 1951. Interpretation of action potentials evoked in the cerebral cortex. *Electroencephalogr Clin Neurophysiol* 3, 449–464. [https://doi.org/10.1016/0013-4694\(51\)90033-8](https://doi.org/10.1016/0013-4694(51)90033-8)
- Echeverria-Altuna, I., Quinn, A.J., Zokaei, N., Woolrich, M.W., Nobre, A.C., van Ede, F., 2022. Transient beta activity and cortico-muscular connectivity during sustained motor behaviour. *Progress in Neurobiology* 214, 102281. <https://doi.org/10.1016/j.pneurobio.2022.102281>
- Edwards, L.J., 2024. Active and passive magnetic shielding for use in OPM-MEG [WWW Document]. URL <https://eprints.nottingham.ac.uk/78714/> (accessed 4.3.25).
- Eisner, J., 2002. An Interactive Spreadsheet for Teaching the Forward-Backward Algorithm, in: *Proceedings of the ACL-02 Workshop on Effective Tools and Methodologies for Teaching Natural Language Processing and Computational Linguistics*. Presented at the TeachingNLP 2002, Association for Computational Linguistics, Philadelphia, Pennsylvania, USA, pp. 10–18. <https://doi.org/10.3115/1118108.1118110>
- Engl, E., Attwell, D., 2015. Non-signalling energy use in the brain. *J Physiol* 593, 3417–3429. <https://doi.org/10.1113/jphysiol.2014.282517>
- Enz, N., Ruddy, K.L., Rueda-Delgado, L.M., Whelan, R., 2021. Volume of β -Bursts, But Not Their Rate, Predicts Successful Response Inhibition. *J Neurosci* 41, 5069–5079. <https://doi.org/10.1523/JNEUROSCI.2231-20.2021>
- Fabricant, A., Novikova, I., Bison, G., 2023. How to build a magnetometer with thermal atomic vapor: a tutorial. *New J. Phys.* 25, 025001. <https://doi.org/10.1088/1367-2630/acb840>
- Faley, M.I., Poppe, U., Urban, K., Paulson, D.N., Starr, T.N., Fagaly, R.L., 2001. Low noise HTS dc-SQUID flip-chip magnetometers and gradiometers. *IEEE Transactions on Applied Superconductivity* 11, 1383–1386. <https://doi.org/10.1109/77.919609>
- Feinberg, D.A., Beckett, A.J.S., Vu, A.T., Stockmann, J., Huber, L., Ma, S., Ahn, S., Setsompop, K., Cao, X., Park, S., Liu, C., Wald, L.L., Polimeni, J.R., Mareyam, A., Gruber, B., Stirnberg, R., Liao, C., Yacoub, E., Davids, M., Bell, P., Rummert, E., Koehler, M., Potthast, A., Gonzalez-Insua, I., Stocker, S., Gunamony, S., Dietz, P., 2023. Next-generation MRI scanner designed for ultra-high-resolution human brain imaging at 7 Tesla. *Nat Methods* 20, 2048–2057. <https://doi.org/10.1038/s41592-023-02068-7>
- Fermi, E., 1930. Über die magnetischen Momente der Atomkerne. *Z. Physik* 60, 320–333. <https://doi.org/10.1007/BF01339933>

- Feynman, R.P. (Richard P., 1918-1988, 1965. The Feynman lectures on physics. Reading, Mass. : Addison-Wesley Pub. Co., c1963-1965.
- Fife, A.A., Vrba, J., Robinson, S.E., Anderson, G., Betts, K., Burbank, M.B., Cheyne, D., Cheung, T., Govorkov, S., Haid, G., Haid, V., Hunter, C., Kubik, P.R., Lee, S., McKay, J., Reichl, E., Schroyen, C., Sekachev, I., Spear, P., Taylor, B., Tillotson, M., Sutherling, W., 1999. Synthetic gradiometer systems for MEG. *IEEE Transactions on Applied Superconductivity* 9, 4063–4068. <https://doi.org/10.1109/77.783919>
- Fox, P.T., Raichle, M.E., 1984. Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. *J Neurophysiol* 51, 1109–1120. <https://doi.org/10.1152/jn.1984.51.5.1109>
- Franzen, W., Emslie, A.G., 1957. Atomic Orientation by Optical Pumping. *Phys. Rev.* 108, 1453–1458. <https://doi.org/10.1103/PhysRev.108.1453>
- Fries, P., 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn Sci* 9, 474–480. <https://doi.org/10.1016/j.tics.2005.08.011>
- Friston, K.J., 2011. Functional and effective connectivity: a review. *Brain Connect* 1, 13–36. <https://doi.org/10.1089/brain.2011.0008>
- Gaetz, W., Rhodes, E., Bloy, L., Blaskey, L., Jackel, C.R., Brodtkin, E.S., Waldman, A., Embick, D., Hall, S., Roberts, T.P.L., 2020. Evaluating motor cortical oscillations and age-related change in autism spectrum disorder. *Neuroimage* 207, 116349. <https://doi.org/10.1016/j.neuroimage.2019.116349>
- Gascoyne, L.E., Brookes, M.J., Rathnaiah, M., Katshu, M.Z.U.H., Koelewijn, L., Williams, G., Kumar, J., Walters, J.T.R., Seedat, Z.A., Palaniyappan, L., Deakin, J.F.W., Singh, K.D., Liddle, P.F., Morris, P.G., 2020. Motor-related oscillatory activity in schizophrenia according to phase of illness and clinical symptom severity. *Neuroimage Clin* 29, 102524. <https://doi.org/10.1016/j.nicl.2020.102524>
- Geselowitz, D., 1970. On the magnetic field generated outside an inhomogeneous volume conductor by internal current sources. *IEEE Transactions on Magnetism* 6, 346–347. <https://doi.org/10.1109/TMAG.1970.1066765>
- Gohil, C., Roberts, E., Timms, R., Skates, A., Higgins, C., Quinn, A., Pervaiz, U., van Amersfoort, J., Notin, P., Gal, Y., Adaszewski, S., Woolrich, M., 2022. Mixtures of large-scale dynamic functional brain network modes. *NeuroImage* 263, 119595. <https://doi.org/10.1016/j.neuroimage.2022.119595>

- Golay, M.J.E., 1958. Field Homogenizing Coils for Nuclear Spin Resonance Instrumentation. *Review of Scientific Instruments* 29, 313–315. <https://doi.org/10.1063/1.1716184>
- Goldman, D.E., 1943. POTENTIAL, IMPEDANCE, AND RECTIFICATION IN MEMBRANES. *J Gen Physiol* 27, 37–60. <https://doi.org/10.1085/jgp.27.1.37>
- Gorgolewski, K.J., Auer, T., Calhoun, V.D., Craddock, R.C., Das, S., Duff, E.P., Flandin, G., Ghosh, S.S., Glatard, T., Halchenko, Y.O., Handwerker, D.A., Hanke, M., Keator, D., Li, X., Michael, Z., Maumet, C., Nichols, B.N., Nichols, T.E., Pellman, J., Poline, J.-B., Rokem, A., Schaefer, G., Sochat, V., Triplett, W., Turner, J.A., Varoquaux, G., Poldrack, R.A., 2016. The brain imaging data structure, a format for organizing and describing outputs of neuroimaging experiments. *Scientific Data* 3, 160044. <https://doi.org/10.1038/sdata.2016.44>
- Gramfort, A., Luessi, M., Larson, E., Engemann, D., Strohmeier, D., Brodbeck, C., Goj, R., Jas, M., Brooks, T., Parkkonen, L., Hämäläinen, M., 2013. MEG and EEG data analysis with MNE-Python. *Frontiers in Neuroscience* 7.
- Gruetter, R., 1993. Automatic, localized in Vivo adjustment of all first-and second-order shim coils. *Magnetic Resonance in Medicine* 29, 804–811. <https://doi.org/10.1002/mrm.1910290613>
- Guido Nolte, 2003. The magnetic lead field theorem in the quasi-static approximation and its use for magnetoencephalography forward calculation in realistic volume conductors. *Physics in Medicine & Biology* 48, 3637. <https://doi.org/10.1088/0031-9155/48/22/002>
- Güllmar, D., Haueisen, J., Reichenbach, J.R., 2010. Influence of anisotropic electrical conductivity in white matter tissue on the EEG/MEG forward and inverse solution. A high-resolution whole head simulation study. *NeuroImage* 51, 145–163. <https://doi.org/10.1016/j.neuroimage.2010.02.014>
- Guskiewicz, K.M., Ross, S.E., Marshall, S.W., 2001. Postural Stability and Neuropsychological Deficits After Concussion in Collegiate Athletes. *J Athl Train* 36, 263–273.
- Hadamard, J., 1902. Sur les problèmes aux dérivés partielles et leur signification physique. *Princeton University Bulletin* 13, 49–52.
- Haft, M., Hofmann, R., Tresp, V., 1999. Model-independent mean-field theory as a local method for approximate propagation of information. *Network: Computation in Neural Systems* 10, 93–105. https://doi.org/10.1088/0954-898X_10_1_006

- Hagen, E., Næss, S., Ness, T.V., Einevoll, G.T., 2018. Multimodal Modeling of Neural Network Activity: Computing LFP, ECoG, EEG, and MEG Signals With LFPy 2.0. *Front. Neuroinform.* 12. <https://doi.org/10.3389/fninf.2018.00092>
- Halgren, E., Raij, T., Marinkovic, K., Jousmäki, V., Hari, R., 2000. Cognitive Response Profile of the Human Fusiform Face Area as Determined by MEG. *Cerebral Cortex* 10, 69–81. <https://doi.org/10.1093/cercor/10.1.69>
- Hämäläinen, M., Hari, R., Ilmoniemi, R.J., Knuutila, J., Lounasmaa, O.V., 1993. Magnetoencephalography---theory, instrumentation, and applications to noninvasive studies of the working human brain. *Rev. Mod. Phys.* 65, 413–497. <https://doi.org/10.1103/RevModPhys.65.413>
- Hammond, P., 1960. Electric and magnetic images. *Proceedings of the IEE - Part C: Monographs* 107, 306–313. <https://doi.org/10.1049/pi-c.1960.0047>
- HAPPER, W., 1972. Optical Pumping. *Rev. Mod. Phys.* 44, 169–249. <https://doi.org/10.1103/RevModPhys.44.169>
- Happer, W., Tang, H., 1973. Spin-exchange shift and narrowing of magnetic resonance lines in optically pumped alkali vapors. *Phys. Rev. Lett.* 31, 273–276. <https://doi.org/10.1103/PhysRevLett.31.273>
- Harmony, T., 2013. The functional significance of delta oscillations in cognitive processing. *Front. Integr. Neurosci.* 7. <https://doi.org/10.3389/fnint.2013.00083>
- Hashimoto, Isao, Mashiko, T., Imada, T., 1996. Somatic evoked high-frequency magnetic oscillations reflect activity of inhibitory interneurons in the human somatosensory cortex. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section* 100, 189–203. [https://doi.org/10.1016/0168-5597\(95\)00244-8](https://doi.org/10.1016/0168-5597(95)00244-8)
- Hashimoto, I., Papuashvili, N., Xu, C., Okada, Y.C., 1996. Neuronal activities from a deep subcortical structure can be detected magnetically outside the brain in the porcine preparation. *Neurosci Lett* 206, 25–28. [https://doi.org/10.1016/0304-3940\(96\)12428-9](https://doi.org/10.1016/0304-3940(96)12428-9)
- Hassan, M.R., Nath, B., 2005. Stock market forecasting using hidden Markov model: a new approach, in: *5th International Conference on Intelligent Systems Design and Applications (ISDA'05)*. Presented at the 5th International Conference on Intelligent Systems Design and Applications (ISDA'05), pp. 192–196. <https://doi.org/10.1109/ISDA.2005.85>
- Haverkamp, I., Mielke, O., Kunert, J., Stolz, R., Meyer, H.-G., Toepfer, H., Ortlepp, T., 2011. Linearity of a Digital SQUID Magnetometer. *IEEE Transactions on Applied Superconductivity* 21, 705–708. <https://doi.org/10.1109/TASC.2010.2087734>

- Heideman, S.G., Quinn, A.J., Woolrich, M.W., van Ede, F., Nobre, A.C., 2020. Dissecting beta-state changes during timed movement preparation in Parkinson's disease. *Prog Neurobiol* 184, 101731. <https://doi.org/10.1016/j.pneurobio.2019.101731>
- Heller, L., van Hulsteyn, D.B., 1992. Brain stimulation using electromagnetic sources: theoretical aspects. *Biophys J* 63, 129–138. [https://doi.org/10.1016/S0006-3495\(92\)81587-4](https://doi.org/10.1016/S0006-3495(92)81587-4)
- Hill, R., Schofield, H., Boto, E., Rier, L., Osborne, J., Doyle, C., Worcester, F., Hayward, T., Holmes, N., Bowtell, R., Shah, V., Brookes, M., 2024. Optimising the Sensitivity of Optically-Pumped Magnetometer Magnetoencephalography to Gamma Band Electrophysiological Activity. *Imaging Neuroscience*. https://doi.org/10.1162/imag_a_00112
- Hill, R.M., Boto, E., Holmes, N., Hartley, C., Seedat, Z.A., Leggett, J., Roberts, G., Shah, V., Tierney, T.M., Woolrich, M.W., Stagg, C.J., Barnes, G.R., Bowtell, R., Slater, R., Brookes, M.J., 2019. A tool for functional brain imaging with lifespan compliance. *Nat Commun* 10, 4785. <https://doi.org/10.1038/s41467-019-12486-x>
- Hill, R.M., Boto, E., Rea, M., Holmes, N., Leggett, J., Coles, L.A., Papastavrou, M., Everton, S.K., Hunt, B.A.E., Sims, D., Osborne, J., Shah, V., Bowtell, R., Brookes, M.J., 2020. Multi-channel whole-head OPM-MEG: Helmet design and a comparison with a conventional system. *NeuroImage* 219, 116995. <https://doi.org/10.1016/j.neuroimage.2020.116995>
- Hill, R.M., Devasagayam, J., Holmes, N., Boto, E., Shah, V., Osborne, J., Safar, K., Worcester, F., Mariani, C., Dawson, E., Woolger, D., Bowtell, R., Taylor, M.J., Brookes, M.J., 2022. Using OPM-MEG in contrasting magnetic environments. *Neuroimage* 253, 119084. <https://doi.org/10.1016/j.neuroimage.2022.119084>
- Hillebrand, A., Barnes, G.R., 2002. A Quantitative Assessment of the Sensitivity of Whole-Head MEG to Activity in the Adult Human Cortex. *NeuroImage* 16, 638–650. <https://doi.org/10.1006/nimg.2002.1102>
- Hobson, P.J., Holmes, N., Patel, P., Styles, B., Chalmers, J., Morley, C., Davis, A., Packer, M., Smith, T.X., Raudonyte, S., Holmes, D., Harrison, R., Woolger, D., Sims, D., Brookes, M.J., Bowtell, R., Fromhold, M., 2023. Benchtop Magnetic Shielding for Benchmarking Atomic Magnetometers. *IEEE Transactions on Instrumentation and Measurement* 72, 1–9. <https://doi.org/10.1109/TIM.2023.3293540>
- Hobson, P.J., Vovrosh, J., Stray, B., Packer, M., Winch, J., Holmes, N., Hayati, F., McGovern, K., Bowtell, R., Brookes, M.J., Bongs, K., Fromhold, T.M., Holynski, M., 2022. Bespoke magnetic field design for a

- magnetically shielded cold atom interferometer. *Sci Rep* 12, 10520. <https://doi.org/10.1038/s41598-022-13979-4>
- Hoburg, J.F., 1995. Principles of quasistatic magnetic shielding with cylindrical and spherical shields. *IEEE Transactions on Electromagnetic Compatibility* 37, 574–579. <https://doi.org/10.1109/15.477342>
- Holmes, N., Bowtell, R., Brookes, M.J., Taulu, S., 2023a. An Iterative Implementation of the Signal Space Separation Method for Magnetoencephalography Systems with Low Channel Counts. *Sensors* 23, 6537. <https://doi.org/10.3390/s23146537>
- Holmes, N., Leggett, J., Boto, E., Roberts, G., Hill, R.M., Tierney, T.M., Shah, V., Barnes, G.R., Brookes, M.J., Bowtell, R., 2018a. A bi-planar coil system for nulling background magnetic fields in scalp mounted magnetoencephalography. *NeuroImage* 181, 760–774. <https://doi.org/10.1016/j.neuroimage.2018.07.028>
- Holmes, N., Leggett, J., Boto, E., Roberts, G., Hill, R.M., Tierney, T.M., Shah, V., Barnes, G.R., Brookes, M.J., Bowtell, R., 2018b. A bi-planar coil system for nulling background magnetic fields in scalp mounted magnetoencephalography. *NeuroImage*. <https://doi.org/10.1016/j.neuroimage.2018.07.028>
- Holmes, N., Leggett, J., Hill, R.M., Rier, L., Boto, E., Schofield, H., Hayward, T., Dawson, E., Woolger, D., Shah, V., Taulu, S., Brookes, M.J., Bowtell, R., 2024. Wearable magnetoencephalography in a lightly shielded environment. *IEEE Trans Biomed Eng PP*. <https://doi.org/10.1109/TBME.2024.3465654>
- Holmes, N., Rea, M., Chalmers, J., Leggett, J., Edwards, L.J., Nell, P., Pink, S., Patel, P., Wood, J., Murby, N., Woolger, D., Dawson, E., Mariani, C., Tierney, T.M., Mellor, S., O'Neill, G.C., Boto, E., Hill, R.M., Shah, V., Osborne, J., Pardington, R., Fierlinger, P., Barnes, G.R., Glover, P., Brookes, M.J., Bowtell, R., 2022. A lightweight magnetically shielded room with active shielding. *Scientific Reports* 12, 13561. <https://doi.org/10.1038/s41598-022-17346-1>
- Holmes, N., Rea, M., Hill, R.M., Leggett, J., Edwards, L.J., Hobson, P.J., Boto, E., Tierney, T.M., Rier, L., Rivero, G.R., Shah, V., Osborne, J., Fromhold, T.M., Glover, P., Brookes, M.J., Bowtell, R., 2023b. Enabling ambulatory movement in wearable magnetoencephalography with matrix coil active magnetic shielding. *Neuroimage* 274, 120157. <https://doi.org/10.1016/j.neuroimage.2023.120157>
- Holmes, N., Tierney, T.M., Leggett, J., Boto, E., Mellor, S., Roberts, G., Hill, R.M., Shah, V., Barnes, G.R., Brookes, M.J., Bowtell, R., 2019a. Balanced, bi-planar magnetic field and field gradient coils for field

- compensation in wearable magnetoencephalography. *Scientific Reports* 9, 14196. <https://doi.org/10.1038/s41598-019-50697-w>
- Holmes, N., Tierney, T.M., Leggett, J., Boto, E., Mellor, S., Roberts, G., Hill, R.M., Shah, V., Barnes, G.R., Brookes, M.J., Bowtell, R., 2019b. Balanced, bi-planar magnetic field and field gradient coils for field compensation in wearable magnetoencephalography. *Scientific Reports*. <https://doi.org/10.1038/s41598-019-50697-w>
- Hoogenboom, N., Schoffelen, J.-M., Oostenveld, R., Parkes, L.M., Fries, P., 2006. Localizing human visual gamma-band activity in frequency, time and space. *NeuroImage* 29, 764–773. <https://doi.org/10.1016/j.neuroimage.2005.08.043>
- Hounsfield, G.N., 1973. Computerized transverse axial scanning (tomography). 1. Description of system. *Br J Radiol* 46, 1016–1022. <https://doi.org/10.1259/0007-1285-46-552-1016>
- Howe, M.W., Atallah, H.E., McCool, A., Gibson, D.J., Graybiel, A.M., 2011. Habit learning is associated with major shifts in frequencies of oscillatory activity and synchronized spike firing in striatum. *Proceedings of the National Academy of Sciences* 108, 16801–16806. <https://doi.org/10.1073/pnas.1113158108>
- Huang, H., Dong, H., Chen, L., Gao, Y., 2016. Single-beam three-axis atomic magnetometer. *Applied Physics Letters* 109, 062404. <https://doi.org/10.1063/1.4960971>
- Huang, H.C., Dong, H.F., Hu, X.Y., Chen, L., Gao, Y., 2015. Three-axis atomic magnetometer based on spin precession modulation. *Applied Physics Letters* 107, 182403. <https://doi.org/10.1063/1.4935096>
- Huang, M.X., Mosher, J.C., Leahy, R.M., 1999. A sensor-weighted overlapping-sphere head model and exhaustive head model comparison for MEG. *Phys Med Biol* 44, 423–440. <https://doi.org/10.1088/0031-9155/44/2/010>
- Iivanainen, J., Borna, A., Zetter, R., Carter, T.R., Stephen, J.M., McKay, J., Parkkonen, L., Taulu, S., Schwindt, P.D.D., 2022. Calibration and Localization of Optically Pumped Magnetometers Using Electromagnetic Coils. *Sensors* 22, 3059. <https://doi.org/10.3390/s22083059>
- Iivanainen, J., Stenroos, M., Parkkonen, L., 2017. Measuring MEG closer to the brain: Performance of on-scalp sensor arrays. *Neuroimage* 147, 542–553. <https://doi.org/10.1016/j.neuroimage.2016.12.048>
- Iivanainen, J., Zetter, R., Grön, M., Hakkarainen, K., Parkkonen, L., 2019a. On-scalp MEG system utilizing an actively shielded array of optically-

- pumped magnetometers. *NeuroImage* 194, 244–258. <https://doi.org/10.1016/j.neuroimage.2019.03.022>
- Iivanainen, J., Zetter, R., Grön, M., Hakkarainen, K., Parkkonen, L., 2019b. On-scalp MEG system utilizing an actively shielded array of optically-pumped magnetometers. *NeuroImage*. <https://doi.org/10.1016/j.neuroimage.2019.03.022>
- Ishiyama, A., Hirooka, H., 1991. Magnetic shielding for MRI superconducting magnets. *IEEE Transactions on Magnetics* 27, 1692–1695. <https://doi.org/10.1109/20.133514>
- Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002a. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 17, 825–841. [https://doi.org/10.1016/s1053-8119\(02\)91132-8](https://doi.org/10.1016/s1053-8119(02)91132-8)
- Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002b. Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage* 17, 825–841. <https://doi.org/10.1006/nimg.2002.1132>
- Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. *Med Image Anal* 5, 143–156. [https://doi.org/10.1016/s1361-8415\(01\)00036-6](https://doi.org/10.1016/s1361-8415(01)00036-6)
- Jensen, O., Kaiser, J., Lachaux, J.-P., 2007. Human gamma-frequency oscillations associated with attention and memory. *Trends Neurosci* 30, 317–324. <https://doi.org/10.1016/j.tins.2007.05.001>
- Jensen, O., Tesche, C.D., 2002. Frontal theta activity in humans increases with memory load in a working memory task. *Eur J Neurosci* 15, 1395–1399. <https://doi.org/10.1046/j.1460-9568.2002.01975.x>
- Jöbsis, F.F., 1977. Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. *Science* 198, 1264–1267. <https://doi.org/10.1126/science.929199>
- Johnson, C., Schwindt, P., Weisend, M., 2010. Magnetoencephalography with a two-color pump-probe, fiber-coupled atomic magnetometer. *Applied Physics Letters* 97, 243703–243703. <https://doi.org/10.1063/1.3522648>
- Jones, S.R., 2016. When brain rhythms aren't 'rhythmic': implication for their mechanisms and meaning. *Current Opinion in Neurobiology, Systems neuroscience* 40, 72–80. <https://doi.org/10.1016/j.conb.2016.06.010>
- Josephson, B.D., 1962. Possible new effects in superconductive tunnelling. *Physics Letters* 1, 251–253. [https://doi.org/10.1016/0031-9163\(62\)91369-0](https://doi.org/10.1016/0031-9163(62)91369-0)

- Juchem, C., Brown, P.B., Nixon, T.W., McIntyre, S., Rothman, D.L., de Graaf, R.A., 2011a. Multicoil shimming of the mouse brain. *Magnetic Resonance in Medicine* 66, 893–900. <https://doi.org/10.1002/mrm.22850>
- Juchem, C., Nixon, T.W., McIntyre, S., Boer, V.O., Rothman, D.L., de Graaf, R.A., 2011b. Dynamic multi-coil shimming of the human brain at 7 T. *J Magn Reson* 212, 280–288. <https://doi.org/10.1016/j.jmr.2011.07.005>
- Juchem, C., Nixon, T.W., McIntyre, S., Rothman, D.L., de Graaf, R.A., 2010. Magnetic field modeling with a set of individual localized coils. *J Magn Reson* 204, 281–289. <https://doi.org/10.1016/j.jmr.2010.03.008>
- Jurafsky, D., Martin, J.H., 2009. *Speech and Language Processing: An Introduction to Natural Language Processing, Computational Linguistics, and Speech Recognition*. Prentice Hall.
- Kajikawa, Y., Schroeder, C.E., 2011. How local is the local field potential? *Neuron* 72, 847–858. <https://doi.org/10.1016/j.neuron.2011.09.029>
- Kamada, K., Sato, D., Ito, Y., Natsukawa, H., Okano, K., Mizutani, N., Kobayashi, T., 2015. Human magnetoencephalogram measurements using newly developed compact module of high-sensitivity atomic magnetometer. *Jpn. J. Appl. Phys.* 54, 026601. <https://doi.org/10.7567/JJAP.54.026601>
- Kanno, A., Nakasato, N., Oogane, M., Fujiwara, K., Nakano, T., Arimoto, T., Matsuzaki, H., Ando, Y., 2022. Scalp attached tangential magnetoencephalography using tunnel magneto-resistive sensors. *Sci Rep* 12, 6106. <https://doi.org/10.1038/s41598-022-10155-6>
- Karvat, G., Schneider, A., Alyahyay, M., Steenbergen, F., Tangermann, M., Diester, I., 2020. Real-time detection of neural oscillation bursts allows behaviourally relevant neurofeedback. *Commun Biol* 3, 1–10. <https://doi.org/10.1038/s42003-020-0801-z>
- Kastler, A., 1973. The Hanle effect and its use for the measurements of very small magnetic fields. *Nuclear Instruments and Methods* 110, 259–265. [https://doi.org/10.1016/0029-554X\(73\)90698-8](https://doi.org/10.1016/0029-554X(73)90698-8)
- Kastler, A., 1951. Méthodes optiques d'étude de la résonance magnétique. *Physica* 17, 191–204. [https://doi.org/10.1016/0031-8914\(51\)90058-4](https://doi.org/10.1016/0031-8914(51)90058-4)
- Kasunic, K.J., 2019. Magnetic Aharonov-Bohm effects and the quantum phase shift: A heuristic interpretation. *American Journal of Physics* 87, 745–751. <https://doi.org/10.1119/1.5115499>
- Katzner, S., Nauhaus, I., Benucci, A., Bonin, V., Ringach, D.L., Carandini, M., 2009. Local origin of field potentials in visual cortex. *Neuron* 61, 35–41. <https://doi.org/10.1016/j.neuron.2008.11.016>

- Kim, J.H., Choi, B.H., Kim, H.R., Rim, C.T., 2019. 2-D Synthesized Magnetic Field Focusing Technology With Loop Coils Distributed in a Rectangular Formation. *IEEE Transactions on Industrial Electronics* 66, 5558–5566. <https://doi.org/10.1109/TIE.2018.2869362>
- Kim, K., Begus, S., Xia, H., Lee, S.K., Jazbinsek, V., Trontelj, Z., Romalis, M.V., 2014. Multi-channel atomic magnetometer for magnetoencephalography: A configuration study. *Neuroimage* 89, 143–151. <https://doi.org/10.1016/j.neuroimage.2013.10.040>
- Kinahan, P.E., Rogers, J.G., 1989. Analytic 3D image reconstruction using all detected events. *IEEE Transactions on Nuclear Science* 36, 964–968. <https://doi.org/10.1109/23.34585>
- King-Casas, B., Tomlin, D., Anen, C., Camerer, C.F., Quartz, S.R., Montague, P.R., 2005. Getting to Know You: Reputation and Trust in a Two-Person Economic Exchange. *Science* 308, 78–83. <https://doi.org/10.1126/science.1108062>
- Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., Schwaiger, J., 1998. Induced alpha band power changes in the human EEG and attention. *Neurosci Lett* 244, 73–76. [https://doi.org/10.1016/s0304-3940\(98\)00122-0](https://doi.org/10.1016/s0304-3940(98)00122-0)
- Klimesch, W., Sauseng, P., Hanslmayr, S., 2007. EEG alpha oscillations: The inhibition–timing hypothesis. *Brain Research Reviews* 53, 63–88. <https://doi.org/10.1016/j.brainresrev.2006.06.003>
- Korth, H., Strohhahn, K., Tejada, F., Andreou, A.G., Kitching, J., Knappe, S., Lehtonen, S.J., London, S.M., Kafel, M., 2016. Miniature atomic scalar magnetometer for space based on the rubidium isotope ⁸⁷Rb. *Journal of Geophysical Research: Space Physics* 121, 7870–7880. <https://doi.org/10.1002/2016JA022389>
- Kutas, M., Federmeier, K.D., 2011. Thirty years and counting: Finding meaning in the N400 component of the event related brain potential (ERP). *Annu Rev Psychol* 62, 621–647. <https://doi.org/10.1146/annurev.psych.093008.131123>
- Kutschka, H., Doeller, C.F., Haueisen, J., Maess, B., 2021. Magnetic field compensation coil design for magnetoencephalography. *Sci Rep* 11, 22650. <https://doi.org/10.1038/s41598-021-01894-z>
- Lauterbur, P.C., 1973. Image Formation by Induced Local Interactions: Examples Employing Nuclear Magnetic Resonance. *Nature* 242, 190–191. <https://doi.org/10.1038/242190a0>
- Law, R.G., Pugliese, S., Shin, H., Sliva, D.D., Lee, S., Neymotin, S., Moore, C., Jones, S.R., 2022. Thalamocortical Mechanisms Regulating the Relationship between Transient Beta Events and Human Tactile

Perception. Cerebral Cortex 32, 668–688.
<https://doi.org/10.1093/cercor/bhab221>

- Leong, V., Byrne, E., Clackson, K., Georgieva, S., Lam, S., Wass, S., 2017. Speaker gaze increases information coupling between infant and adult brains. *Proceedings of the National Academy of Sciences* 114, 13290–13295. <https://doi.org/10.1073/pnas.1702493114>
- Li, H., Zhang, S.-L., Zhang, C.-X., Kong, X.-Y., Xie, X.-M., 2016. An efficient calibration method for SQUID measurement system using three orthogonal Helmholtz coils*. *Chinese Phys. B* 25, 068501. <https://doi.org/10.1088/1674-1056/25/6/068501>
- Little, S., Bonaiuto, J., Barnes, G., Bestmann, S., 2019. Human motor cortical beta bursts relate to movement planning and response errors. *PLoS Biol* 17, e3000479. <https://doi.org/10.1371/journal.pbio.3000479>
- Little, S., Brown, P., 2014. The functional role of beta oscillations in Parkinson's disease. *Parkinsonism Relat Disord* 20 Suppl 1, S44-48. [https://doi.org/10.1016/S1353-8020\(13\)70013-0](https://doi.org/10.1016/S1353-8020(13)70013-0)
- Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A., 2001. Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412, 150–157. <https://doi.org/10.1038/35084005>
- LORENTE de NO, R., 1947. Analysis of the distribution of the action currents of nerve in volume conductors. *Stud Rockefeller Inst Med Res Repr* 132, 384–477.
- Löwdin, P., 1950. On the Non-Orthogonality Problem Connected with the Use of Atomic Wave Functions in the Theory of Molecules and Crystals. *The Journal of Chemical Physics* 18, 365–375. <https://doi.org/10.1063/1.1747632>
- Luck, S., 2005. *An Introduction to The Event-Related Potential Technique*, Cambridge.
- Mager, A., 1970. Magnetic shields. *IEEE Transactions on Magnetics* 6, 67–75. <https://doi.org/10.1109/TMAG.1970.1066714>
- Mandal, P.K., Banerjee, A., Tripathi, M., Sharma, A., 2018. A Comprehensive Review of Magnetoencephalography (MEG) Studies for Brain Functionality in Healthy Aging and Alzheimer's Disease (AD). *Front Comput Neurosci* 12, 60. <https://doi.org/10.3389/fncom.2018.00060>
- Mansfield, P., Grannell, P.K., 1973. NMR “diffraction” in solids? *J. Phys. C: Solid State Phys.* 6, L422. <https://doi.org/10.1088/0022-3719/6/22/007>
- Marhl, U., Jodko-Włodzińska, A., Brühl, R., Sander, T., Jazbinšek, V., 2022. Transforming and comparing data between standard SQUID and OPM-

MEG systems. PLoS ONE 17, 1–22.
<https://doi.org/10.1371/journal.pone.0262669>

Markowitz, W., Hall, R.G., Essen, L., Parry, J.V.L., 1958. Frequency of Cesium in Terms of Ephemeris Time. *Phys. Rev. Lett.* 1, 105–107.
<https://doi.org/10.1103/PhysRevLett.1.105>

Markus Bauer, Robert Oostenveld, Maarten Peeters, Pascal Fries, 2006. Tactile Spatial Attention Enhances Gamma-Band Activity in Somatosensory Cortex and Reduces Low-Frequency Activity in Parieto-Occipital Areas. *J. Neurosci.* 26, 490. <https://doi.org/10.1523/JNEUROSCI.5228-04.2006>

Martens, M.A., Petropoulos, L.S., Brown, R.W., Andrews, J.H., Morich, M.A., Patrick, J.L., 1991. Insertable biplanar gradient coils for magnetic resonance imaging. *Review of Scientific Instruments* 62, 2639–2645.
<https://doi.org/10.1063/1.1142245>

Masuzawa, M., Terashima, A., Tsuchiya, K., 2013. Magnetic Shielding: Our Experience with Various Shielding Materials.

Mazziotta, J., Toga, A., Evans, A., Fox, P., Lancaster, J., Zilles, K., Woods, R., Paus, T., Simpson, G., Pike, B., Holmes, C., Collins, L., Thompson, P., MacDonald, D., Iacoboni, M., Schormann, T., Amunts, K., Palomero-Gallagher, N., Geyer, S., Parsons, L., Narr, K., Kabani, N., Goualher, G.L., Boomsma, D., Cannon, T., Kawashima, R., Mazoyer, B., 2001. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philosophical Transactions of the Royal Society of London. Series B* 356, 1293.
<https://doi.org/10.1098/rstb.2001.0915>

Mellor, S., Tierney, T.M., O'Neill, G.C., Alexander, N., Seymour, R.A., Holmes, N., Lopez, J.D., Hill, R.M., Boto, E., Rea, M., Roberts, G., Leggett, J., Bowtell, R., Brookes, M.J., Maguire, E.A., Walker, M.C., Barnes, G.R., 2022. Magnetic Field Mapping and Correction for Moving OP-MEG. *IEEE Trans. Biomed. Eng.* 69, 528–536.
<https://doi.org/10.1109/TBME.2021.3100770>

Mellor, S., Tierney, T.M., O'Neill, G.C., Alexander, N., Seymour, R.A., Holmes, N., López, J.D., Hill, R.M., Boto, E., Rea, M., Roberts, G., Leggett, J., Bowtell, R., Brookes, M.J., Maguire, E.A., Walker, M.C., Barnes, G.R., 2021. Magnetic Field Mapping and Correction for Moving OP-MEG. <https://doi.org/10.1101/2021.05.25.444975>

Mercier, J., 2011. Flux quantization [WWW Document]. *Supraconductivite*. URL <https://www.supraconductivite.fr/en/applications-squid-quantification.php> (accessed 1.22.25).

Milonni, P.W., Eberly, J.H., 2010. *Laser physics*. Wiley.

- Mishra, S.S., Loloee, R., Birge, N.O., 2023. Effect of interfaces on supercurrent through ferromagnetic materials. *IEEE Trans. Appl. Supercond.* 33, 1–7. <https://doi.org/10.1109/TASC.2023.3289838>
- Montague, P.R., Berns, G.S., Cohen, J.D., McClure, S.M., Pagnoni, G., Dhamala, M., Wiest, M.C., Karpov, I., King, R.D., Apple, N., Fisher, R.E., 2002. Hyperscanning: Simultaneous fMRI during Linked Social Interactions. *NeuroImage* 16, 1159–1164. <https://doi.org/10.1006/nimg.2002.1150>
- Morris, M.E., Huxham, F., McGinley, J., Dodd, K., Iansek, R., 2001. The biomechanics and motor control of gait in Parkinson disease. *Clinical Biomechanics* 16, 459–470. [https://doi.org/10.1016/S0268-0033\(01\)00035-3](https://doi.org/10.1016/S0268-0033(01)00035-3)
- Murakami, S., Okada, Y., 2006. Contributions of principal neocortical neurons to magnetoencephalography and electroencephalography signals. *J Physiol* 575, 925–936. <https://doi.org/10.1113/jphysiol.2006.105379>
- Muthukumaraswamy, S., 2013. High-frequency brain activity and muscle artifacts in MEG/EEG: A review and recommendations. *Front. Hum. Neurosci.* 7. <https://doi.org/10.3389/fnhum.2013.00138>
- Nardelli, N.V., Krzyzewski, S.P., Knappe, S.A., 2019. Reducing crosstalk in optically-pumped magnetometer arrays. *Phys. Med. Biol.* 64, 21NT03. <https://doi.org/10.1088/1361-6560/ab4c06>
- Neymotin, S.A., Daniels, D.S., Caldwell, B., McDougal, R.A., Carnevale, N.T., Jas, M., Moore, C.I., Hines, M.L., Hämäläinen, M., Jones, S.R., 2020. Human Neocortical Neurosolver (HNN), a new software tool for interpreting the cellular and network origin of human MEG/EEG data. *Elife* 9, e51214. <https://doi.org/10.7554/eLife.51214>
- Nugent, A.C., Benitez Andonegui, A., Holroyd, T., Robinson, S.E., 2022. On-scalp magnetocorticography with optically pumped magnetometers: Simulated performance in resolving simultaneous sources. *Neuroimage: Reports* 2, 100093. <https://doi.org/10.1016/j.ynirp.2022.100093>
- Nugent, A.C., Robinson, S.E., Coppola, R., Furey, M.L., Zarate, C.A., 2015. Group differences in MEG-ICA derived resting state networks: Application to major depressive disorder. *Neuroimage* 118, 1–12. <https://doi.org/10.1016/j.neuroimage.2015.05.051>
- Nurminen, J., Taulu, S., Nenonen, J., Helle, L., Simola, J., Ahonen, A., 2013. Improving MEG Performance With Additional Tangential Sensors. *IEEE Transactions on Biomedical Engineering* 60, 2559–2566. <https://doi.org/10.1109/TBME.2013.2260541>

- Nurminen, J., Taulu, S., Okada, Y., 2008. Effects of sensor calibration, balancing and parametrization on the signal space separation method. *Phys. Med. Biol.* 53, 1975. <https://doi.org/10.1088/0031-9155/53/7/012>
- Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A* 87, 9868–9872.
- Öisjöen, F., Schneiderman, J.F., Figueras, G.A., Chukharkin, M.L., Kalabukhov, A., Hedström, A., Elam, M., Winkler, D., 2012. High-Tc superconducting quantum interference device recordings of spontaneous brain activity: Towards high-Tc magnetoencephalography. *Applied Physics Letters* 100, 132601. <https://doi.org/10.1063/1.3698152>
- O'Neill, G.C., Bauer, M., Woolrich, M.W., Morris, P.G., Barnes, G.R., Brookes, M.J., 2015. Dynamic recruitment of resting state sub-networks. *NeuroImage* 115, 85–95. <https://doi.org/10.1016/j.neuroimage.2015.04.030>
- O'Neill, G.C., Tewarie, P., Vidaurre, D., Liuzzi, L., Woolrich, M.W., Brookes, M.J., 2018. Dynamics of large-scale electrophysiological networks: A technical review. *Neuroimage* 180, 559–576. <https://doi.org/10.1016/j.neuroimage.2017.10.003>
- Onton, J., Delorme, A., Makeig, S., 2005. Frontal midline EEG dynamics during working memory. *Neuroimage* 27, 341–356. <https://doi.org/10.1016/j.neuroimage.2005.04.014>
- Oostenveld, R., Fries, P., Maris, E., Schoffelen, J.-M., 2010. FieldTrip: Open Source Software for Advanced Analysis of MEG, EEG, and Invasive Electrophysiological Data. *Computational Intelligence and Neuroscience* 2011, e156869. <https://doi.org/10.1155/2011/156869>
- Osborne, J., Orton, J., Alem, O., Shah, V., 2018. Fully integrated standalone zero field optically pumped magnetometer for biomagnetism, in: *Steep Dispersion Engineering and Opto-Atomic Precision Metrology XI*. Presented at the Steep Dispersion Engineering and Opto-Atomic Precision Metrology XI, SPIE, pp. 89–95. <https://doi.org/10.1117/12.2299197>
- Oyama, D., Adachi, Y., Higuchi, M., Uehara, G., 2022. Calibration of a Coil Array Geometry Using an X-Ray Computed Tomography. *IEEE Transactions on Magnetism* 58, 1–5. <https://doi.org/10.1109/TMAG.2021.3080673>
- Oyama, D., Adachi, Y., Yumoto, M., Hashimoto, I., Uehara, G., 2015. Dry phantom for magnetoencephalography —Configuration, calibration, and contribution. *Journal of Neuroscience Methods* 251, 24–36. <https://doi.org/10.1016/j.jneumeth.2015.05.004>

- Packer, M., Hobson, P.J., Davis, A., Holmes, N., Leggett, J., Glover, P., Hardwicke, N.L., Brookes, M.J., Bowtell, R., Fromhold, T.M., 2022. Magnetic field design in a cylindrical high-permeability shield: The combination of simple building blocks and a genetic algorithm. *Journal of Applied Physics* 131, 093902. <https://doi.org/10.1063/5.0071986>
- Packer, M., Hobson, P.J., Holmes, N., Leggett, J., Glover, P., Brookes, M.J., Bowtell, R., Fromhold, T.M., 2020. Optimal Inverse Design of Magnetic Field Profiles in a Magnetically Shielded Cylinder. *Phys. Rev. Appl.* 14, 054004. <https://doi.org/10.1103/PhysRevApplied.14.054004>
- Palva, S., Palva, J.M., 2012. Discovering oscillatory interaction networks with M/EEG: challenges and breakthroughs. *Trends Cogn Sci* 16, 219–230. <https://doi.org/10.1016/j.tics.2012.02.004>
- Park, C.J., Hong, S.B., 2019. High Frequency Oscillations in Epilepsy: Detection Methods and Considerations in Clinical Application. *J Epilepsy Res* 9, 1–13. <https://doi.org/10.14581/jer.19001>
- Peirce, J., Gray, J.R., Simpson, S., MacAskill, M., Höchenberger, R., Sogo, H., Kastman, E., Lindeløv, J.K., 2019. PsychoPy2: Experiments in behavior made easy. *Behav Res* 51, 195–203. <https://doi.org/10.3758/s13428-018-01193-y>
- Penny, W.D., Roberts, S.J., 2002. Bayesian multivariate autoregressive models with structured priors. *IEE Proceedings: Vision, Image and Signal Processing* 149, 33–41. <https://doi.org/10.1049/ip-vis:20020149>
- Petrashov, V.T., Antonov, V.N., Delsing, P., Claeson, T., 1995. Phase Controlled Conductance of Mesoscopic Structures with Superconducting ``Mirrors''. *Phys. Rev. Lett.* 74, 5268–5271. <https://doi.org/10.1103/PhysRevLett.74.5268>
- Petrashov, V.T., Chua, K.G., Marshall, K.M., Shaikhaidarov, R.Sh., Nicholls, J.T., 2005. Andreev Probe of Persistent Current States in Superconducting Quantum Circuits. *Phys. Rev. Lett.* 95, 147001. <https://doi.org/10.1103/PhysRevLett.95.147001>
- Pfeiffer, C., Andersen, L.M., Lundqvist, D., Hämäläinen, M., Schneiderman, J.F., Oostenveld, R., 2018. Localizing on-scalp MEG sensors using an array of magnetic dipole coils. *PLOS ONE* 13, e0191111. <https://doi.org/10.1371/journal.pone.0191111>
- Pfeiffer, C., Ruffieux, S., Andersen, L.M., Kalabukhov, A., Winkler, D., Oostenveld, R., Lundqvist, D., Schneiderman, J.F., 2020. On-scalp MEG sensor localization using magnetic dipole-like coils: A method for highly accurate co-registration. *NeuroImage* 212, 116686. <https://doi.org/10.1016/j.neuroimage.2020.116686>

- Pfeiffer, C., Ruffieux, S., Jönsson, L., Chukharkin, M.L., Kalaboukhov, A., Xie, M., Winkler, D., Schneiderman, J.F., 2019. A 7-channel high-Tc SQUID-based on-scalp MEG system. <https://doi.org/10.1101/534107>
- Pfurtscheller, G., Lopes da Silva, F.H., 1999. Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clinical Neurophysiology* 110, 1842–1857. [https://doi.org/10.1016/S1388-2457\(99\)00141-8](https://doi.org/10.1016/S1388-2457(99)00141-8)
- Picton, T. w., Bentin, S., Berg, P., Donchin, E., Hillyard, S. a., Johnson JR., R., Miller, G. a., Ritter, W., Ruchkin, D. s., Rugg, M. d., Taylor, M. j., 2000. Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology* 37, 127–152. <https://doi.org/10.1111/1469-8986.3720127>
- Quinn, A.J., van Ede, F., Brookes, M.J., Heideman, S.G., Nowak, M., Seedat, Z.A., Vidaurre, D., Zich, C., Nobre, A.C., Woolrich, M.W., 2019. Unpacking Transient Event Dynamics in Electrophysiological Power Spectra. *Brain Topography* 32, 1020–1034. <https://doi.org/10.1007/s10548-019-00745-5>
- Quinn, A.J., Vidaurre, D., Abeysuriya, R., Becker, R., Nobre, A.C., Woolrich, M.W., 2018. Task-Evoked Dynamic Network Analysis Through Hidden Markov Modeling. *Front. Neurosci.* 12. <https://doi.org/10.3389/fnins.2018.00603>
- Rabiner, L.R., 1989. A tutorial on hidden Markov models and selected applications in speech recognition. *Proceedings of the IEEE* 77, 257–286. <https://doi.org/10.1109/5.18626>
- Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. *Proc Natl Acad Sci U S A* 98, 676–682. <https://doi.org/10.1073/pnas.98.2.676>
- Rampp, S., Stefan, H., Wu, X., Kaltenhäuser, M., Maess, B., Schmitt, F.C., Wolters, C.H., Hamer, H., Kasper, B.S., Schwab, S., Doerfler, A., Blümcke, I., Rössler, K., Buchfelder, M., 2019. Magnetoencephalography for epileptic focus localization in a series of 1000 cases. *Brain* 142, 3059–3071. <https://doi.org/10.1093/brain/awz231>
- Rangaraju, V., Calloway, N., Ryan, T.A., 2014. Activity-driven local ATP synthesis is required for synaptic function. *Cell* 156, 825–835. <https://doi.org/10.1016/j.cell.2013.12.042>
- Rayson, H., Szul, M.J., El-Khoueiry, P., Debnath, R., Gautier-Martins, M., Ferrari, P.F., Fox, N., Bonaiuto, J.J., 2023. Bursting with Potential: How Sensorimotor Beta Bursts Develop from Infancy to Adulthood. *J Neurosci* 43, 8487–8503. <https://doi.org/10.1523/JNEUROSCI.0886-23.2023>

- Rea, M., Boto, E., Holmes, N., Hill, R., Osborne, J., Rhodes, N., Leggett, J., Rier, L., Bowtell, R., Shah, V., Brookes, M.J., 2022. A 90-channel triaxial magnetoencephalography system using optically pumped magnetometers. *Annals of the New York Academy of Sciences* 1517, 107–124. <https://doi.org/10.1111/nyas.14890>
- Rea, M., Holmes, N., Hill, R.M., Boto, E., Leggett, J., Edwards, L.J., Woolger, D., Dawson, E., Shah, V., Osborne, J., Bowtell, R., Brookes, M.J., 2021a. Precision magnetic field modelling and control for wearable magnetoencephalography. *NeuroImage* 241, 118401. <https://doi.org/10.1016/j.neuroimage.2021.118401>
- Rea, M., Holmes, N., Hill, R.M., Boto, E., Leggett, J., Edwards, L.J., Woolger, D., Dawson, E., Shah, V., Osborne, J., Bowtell, R., Brookes, M.J., 2021b. Precision magnetic field modelling and control for wearable magnetoencephalography. *NeuroImage* 241, 118401. <https://doi.org/10.1016/j.neuroimage.2021.118401>
- Reite, M., Edrich, J., Zimmerman, J.T., Zimmerman, J.E., 1978. Human magnetic auditory evoked fields. *Electroencephalography and Clinical Neurophysiology* 45, 114–117. [https://doi.org/10.1016/0013-4694\(78\)90349-8](https://doi.org/10.1016/0013-4694(78)90349-8)
- Rezek, I., Roberts, S., 2005. Ensemble Hidden Markov Models with Extended Observation Densities for Biosignal Analysis, in: Husmeier, D., Dybowski, R., Roberts, S. (Eds.), *Probabilistic Modeling in Bioinformatics and Medical Informatics*. Springer, London, pp. 419–450. https://doi.org/10.1007/1-84628-119-9_14
- Rhodes, N., Rea, M., Boto, E., Rier, L., Shah, V., Hill, R.M., Osborne, J., Doyle, C., Holmes, N., Coleman, S.C., Mullinger, K., Bowtell, R., Brookes, M.J., 2023. Measurement of Frontal Midline Theta Oscillations using OPM-MEG. *Neuroimage* 271, 120024. <https://doi.org/10.1016/j.neuroimage.2023.120024>
- Riaz, B., Pfeiffer, C., Schneiderman, J.F., 2017. Evaluation of realistic layouts for next generation on-scalp MEG: spatial information density maps. *Sci Rep* 7, 6974. <https://doi.org/10.1038/s41598-017-07046-6>
- Riedner, B.A., Vyazovskiy, V.V., Huber, R., Massimini, M., Esser, S., Murphy, M., Tononi, G., 2007. Sleep Homeostasis and Cortical Synchronization: III. A High-Density EEG Study of Sleep Slow Waves in Humans. *Sleep* 30, 1643–1657. <https://doi.org/10.1093/sleep/30.12.1643>
- Rier, L., Rhodes, N., Pakenham, D., Boto, E., Holmes, N., Hill, R.M., Rivero, G.R., Shah, V., Doyle, C., Osborne, J., Bowtell, R., Taylor, M.J., Brookes, M.J., 2024. The neurodevelopmental trajectory of beta band oscillations: an OPM-MEG study. *eLife* 13. <https://doi.org/10.7554/eLife.94561.1>

- Rier, L., Zamyadi, R., Zhang, J., Emami, Z., Seedat, Z.A., Mocanu, S., Gascoyne, L.E., Allen, C.M., Scadding, J.W., Furlong, P.L., Gooding-Williams, G., Woolrich, M.W., Evangelou, N., Brookes, M.J., Dunkley, B.T., 2021. Mild traumatic brain injury impairs the coordination of intrinsic and motor-related neural dynamics. *Neuroimage Clin* 32, 102841. <https://doi.org/10.1016/j.nicl.2021.102841>
- Roberts, G., Holmes, N., Alexander, N., Boto, E., Leggett, J., Hill, R.M., Shah, V., Rea, M., Vaughan, R., Maguire, E.A., Kessler, K., Beebe, S., Fromhold, M., Barnes, G.R., Bowtell, R., Brookes, M.J., 2019. Towards OPM-MEG in a virtual reality environment. *NeuroImage* 199, 408–417. <https://doi.org/10.1016/j.neuroimage.2019.06.010>
- Robinson, S., 1999. Functional neuroimaging by Synthetic Aperture Magnetometry (SAM).
- Robinson, S.E., Andonegui, A.B., Holroyd, T., Hughes, K.J., Alem, O., Knappe, S., Maydew, T., Griesshammer, A., Nugent, A., 2022. Cross-Axis Dynamic Field Compensation of Optically Pumped Magnetometer Arrays for MEG. *NeuroImage* 262, 119559. <https://doi.org/10.1016/j.neuroimage.2022.119559>
- Robson, S.E., Brookes, M.J., Hall, E.L., Palaniyappan, L., Kumar, J., Skelton, M., Christodoulou, N.G., Qureshi, A., Jan, F., Katshu, M.Z., Liddle, E.B., Liddle, P.F., Morris, P.G., 2016. Abnormal visuomotor processing in schizophrenia. *Neuroimage Clin* 12, 869–878. <https://doi.org/10.1016/j.nicl.2015.08.005>
- Roméo, F., Hoult, D.I., 1984. Magnet field profiling: Analysis and correcting coil design. *Magnetic Resonance in Medicine* 1, 44–65. <https://doi.org/10.1002/mrm.1910010107>
- Ronconi, L., Vitale, A., Federici, A., Pini, E., Molteni, M., Casartelli, L., 2020. Altered neural oscillations and connectivity in the beta band underlie detail-oriented visual processing in autism. *Neuroimage Clin* 28, 102484. <https://doi.org/10.1016/j.nicl.2020.102484>
- Rondin, L., Tetienne, J.-P., Hingant, T., Roch, J.-F., Maletinsky, P., Jacques, V., 2014. Magnetometry with nitrogen-vacancy defects in diamond. *Rep. Prog. Phys.* 77, 056503. <https://doi.org/10.1088/0034-4885/77/5/056503>
- Rong, F., Contreras-Vidal, J.L., 2006. Magnetoencephalographic artifact identification and automatic removal based on independent component analysis and categorization approaches. *Journal of Neuroscience Methods* 157, 337–354. <https://doi.org/10.1016/j.jneumeth.2006.04.024>
- Roshen, W.A., 1990. Effect of finite thickness of magnetic substrate on planar inductors. *IEEE Transactions on Magnetics* 26, 270–275. <https://doi.org/10.1109/20.50553>

- Rosner, M., Beck, D., Fierlinger, P., Filter, H., Klau, C., Kuchler, F., Rößner, P., Sturm, M., Wurm, D., Sun, Z., 2022. A highly drift-stable atomic magnetometer for fundamental physics experiments. *Applied Physics Letters* 120, 161102. <https://doi.org/10.1063/5.0083854>
- Saby, J.N., Marshall, P.J., 2012. The utility of EEG band power analysis in the study of infancy and early childhood. *Dev Neuropsychol* 37, 253–273. <https://doi.org/10.1080/87565641.2011.614663>
- Safar, K., Vandewouw, M.M., Sato, J., Devasagayam, J., Hill, R.M., Rea, M., Brookes, M.J., Taylor, M.J., 2024. Using optically pumped magnetometers to replicate task-related responses in next generation magnetoencephalography. *Sci Rep* 14, 6513. <https://doi.org/10.1038/s41598-024-56878-6>
- Sander, T.H., Preusser, J., Mhaskar, R., Kitching, J., Trahms, L., Knappe, S., 2012. Magnetoencephalography with a chip-scale atomic magnetometer. *Biomed. Opt. Express*, BOE 3, 981–990. <https://doi.org/10.1364/BOE.3.000981>
- Sareen, E., Zahar, S., Ville, D.V.D., Gupta, A., Griffa, A., Amico, E., 2021. Exploring MEG brain fingerprints: Evaluation, pitfalls, and interpretations. *NeuroImage* 240, 118331. <https://doi.org/10.1016/j.neuroimage.2021.118331>
- Sarvas, J., 1987. Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem. *Phys Med Biol* 32, 11–22. <https://doi.org/10.1088/0031-9155/32/1/004>
- Savukov, I.M., Romalis, M.V., 2005a. NMR Detection with an Atomic Magnetometer. *Phys. Rev. Lett.* 94, 123001. <https://doi.org/10.1103/PhysRevLett.94.123001>
- Savukov, I.M., Romalis, M.V., 2005b. Effects of spin-exchange collisions in a high-density alkali-metal vapor in low magnetic fields. *Phys. Rev. A* 71, 023405. <https://doi.org/10.1103/PhysRevA.71.023405>
- Schoffelen, J.-M., Gross, J., 2009. Source connectivity analysis with MEG and EEG. *Hum Brain Mapp* 30, 1857–1865. <https://doi.org/10.1002/hbm.20745>
- Schofield, H., Boto, E., Shah, V., Hill, R.M., Osborne, J., Rea, M., Doyle, C., Holmes, N., Bowtell, R., Woolger, D., Brookes, M.J., 2022. Quantum enabled functional neuroimaging: the why and how of magnetoencephalography using optically pumped magnetometers. *Contemp. Phys.* 63, 161–179. <https://doi.org/10.1080/00107514.2023.2182950>
- Schofield, H., Hill, R.M., Feys, O.M., Holmes, N., Osborne, J., Doyle, C., Bobela, D., Corvilain, P., Wens, V., Rier, L., Bowtell, R., Ferez, M.,

- Mullinger, K.J., Coleman, S., Rhodes, N., Rea, M., Tanner, Z., Boto, E., Tiege, X.D., Shah, V., Brookes, M.J., 2024. A Novel, Robust, and Portable Platform for Magnetoencephalography using Optically Pumped Magnetometers. <https://doi.org/10.1101/2024.03.06.583313>
- Schwindt, P.D.D., Lindseth, B., Knappe, S., Shah, V., Kitching, J., Liew, L.-A., 2007. Chip-scale atomic magnetometer with improved sensitivity by use of the Mx technique. *Applied Physics Letters* 90, 081102. <https://doi.org/10.1063/1.2709532>
- Scofield, J.H., 1994. Frequency-domain description of a lock-in amplifier. *American Journal of Physics* 62, 129–133. <https://doi.org/10.1119/1.17629>
- Scott, A., 1982. Neurophysics, in: Teplitz, D. (Ed.), *Electromagnetism: Paths to Research*. Springer US, Boston, MA, pp. 109–135. https://doi.org/10.1007/978-1-4757-0650-5_3
- Scott, B.S., 1977. Adult mouse dorsal root ganglia neurons in cell culture. *Journal of Neurobiology* 8, 417–427. <https://doi.org/10.1002/neu.480080503>
- Seedat, Z.A., Pier, K.S., Holmes, N., Rea, M., Al-Hilaly, L., Tierney, T.M., Pardington, R., Mullinger, K.J., Cross, J.H., Boto, E., Brookes, M.J., 2023a. Simultaneous whole-head electrophysiological recordings using EEG and OPM-MEG. <https://doi.org/10.1101/2023.10.22.23297153>
- Seedat, Z.A., Quinn, A.J., Vidaurre, D., Liuzzi, L., Gascoyne, L.E., Hunt, B.A.E., O'Neill, G.C., Pakenham, D.O., Mullinger, K.J., Morris, P.G., Woolrich, M.W., Brookes, M.J., 2020. The role of transient spectral ‘bursts’ in functional connectivity: A magnetoencephalography study. *NeuroImage* 209, 116537. <https://doi.org/10.1016/j.neuroimage.2020.116537>
- Seedat, Z.A., Rier, L., Gascoyne, L.E., Cook, H., Woolrich, M.W., Quinn, A.J., Roberts, T.P.L., Furlong, P.L., Armstrong, C., St Pier, K., Mullinger, K.J., Marsh, E.D., Brookes, M.J., Gaetz, W., 2023b. Mapping Interictal activity in epilepsy using a hidden Markov model: A magnetoencephalography study. *Hum. Brain Mapp.* 44, 66–81. <https://doi.org/10.1002/hbm.26118>
- Sekihara, K., Nagarajan, S.S., Poeppel, D., Marantz, A., 2004. Asymptotic SNR of scalar and vector minimum-variance beamformers for neuromagnetic source reconstruction. *IEEE Transactions on Biomedical Engineering* 51, 1726–1734. <https://doi.org/10.1109/TBME.2004.827926>
- Seltzer, S.J., 2008. *Developments in alkali -metal atomic magnetometry* (Ph.D.). ProQuest Dissertations and Theses. Princeton University, United States -- New Jersey.

- Seltzer, S.J., Romalis, M.V., 2004. Unshielded three-axis vector operation of a spin-exchange-relaxation-free atomic magnetometer. *Applied Physics Letters* 85, 4804–4806. <https://doi.org/10.1063/1.1814434>
- Seo, D., Carmena, J.M., Rabaey, J.M., Maharbiz, M.M., Alon, E., 2015. Model validation of untethered, ultrasonic neural dust motes for cortical recording. *Journal of Neuroscience Methods, Brain Computer Interfaces; Tribute to Greg A. Gerhardt* 244, 114–122. <https://doi.org/10.1016/j.jneumeth.2014.07.025>
- Seymour, R.A., Alexander, N., Mellor, S., O'Neill, G.C., Tierney, T.M., Barnes, G.R., Maguire, E.A., 2022. Interference suppression techniques for OPM-based MEG: Opportunities and challenges. *NeuroImage* 247, 118834. <https://doi.org/10.1016/j.neuroimage.2021.118834>
- Seymour, R.A., Alexander, N., Mellor, S., O'Neill, G.C., Tierney, T.M., Barnes, G.R., Maguire, E.A., 2021. Using OPMs to measure neural activity in standing, mobile participants. *NeuroImage* 244, 118604. <https://doi.org/10.1016/j.neuroimage.2021.118604>
- Shah, V., Doyle, C., Osborne, J., 2020. Zero field parametric resonance magnetometer with triaxial sensitivity. US10775450B1.
- Shah, V., Hughes, K.J., 2015. Method for detecting zero-field resonance. US9116201B2.
- Shah, V., Knappe, S., Schwindt, P.D.D., Kitching, J., 2007. Subpicotesla atomic magnetometry with a microfabricated vapour cell. *Nature Photon* 1, 649–652. <https://doi.org/10.1038/nphoton.2007.201>
- Shah, V., Romalis, M.V., 2009. Spin-exchange relaxation-free magnetometry using elliptically polarized light. *Phys. Rev. A* 80, 013416. <https://doi.org/10.1103/PhysRevA.80.013416>
- Shah, V.K., Wakai, R.T., 2013. A compact, high performance atomic magnetometer for biomedical applications. *Phys. Med. Biol.* 58, 8153. <https://doi.org/10.1088/0031-9155/58/22/8153>
- Shelly, C.D., Matrozova, E.A., Petrashov, V.T., 2016. Resolving thermoelectric paradox in superconductors. *Sci. Adv.* 2, e1501250. <https://doi.org/10.1126/sciadv.1501250>
- Sherman, M.A., Lee, S., Law, R., Haegens, S., Thorn, C.A., Hämäläinen, M.S., Moore, C.I., Jones, S.R., 2016. Neural mechanisms of transient neocortical beta rhythms: Converging evidence from humans, computational modeling, monkeys, and mice. *Proceedings of the National Academy of Sciences* 113, E4885–E4894. <https://doi.org/10.1073/pnas.1604135113>

- Shi, F., Zhang, Q., Wang, P., Sun, H., Wang, Jiarong, Rong, X., Chen, M., Ju, C., Reinhard, F., Chen, H., Wrachtrup, J., Wang, Junfeng, Du, J., 2015. Protein imaging. Single-protein spin resonance spectroscopy under ambient conditions. *Science* 347, 1135–1138. <https://doi.org/10.1126/science.aaa2253>
- Shin, H., Law, R., Tsutsui, S., Moore, C.I., Jones, S.R., 2017. The rate of transient beta frequency events predicts behavior across tasks and species. *eLife* 6, e29086. <https://doi.org/10.7554/eLife.29086>
- Slocum, R.E., Reilly, F.N., 1963. Low Field Helium Magnetometer for Space Applications. *IEEE Transactions on Nuclear Science* 10, 165–171. <https://doi.org/10.1109/TNS.1963.4323257>
- Spasojević, D., Janićević, S., Tadić, B., 2024. Hysteresis-loop phenomena in disordered ferromagnets with demagnetizing field and finite temperature. *Phys. Rev. E* 110, 014133. <https://doi.org/10.1103/PhysRevE.110.014133>
- Sporn, S., Hein, T., Herrojo Ruiz, M., 2020. Alterations in the amplitude and burst rate of beta oscillations impair reward-dependent motor learning in anxiety. *eLife* 9, e50654. <https://doi.org/10.7554/eLife.50654>
- Squire, L., 2012. *Fundamental neuroscience*. Academic Press.
- Steck, D., 2003. Rubidium 87 D Line Data.
- Stenroos, M., Hunold, A., Haueisen, J., 2014. Comparison of three-shell and simplified volume conductor models in magnetoencephalography. *Neuroimage* 94, 337–348. <https://doi.org/10.1016/j.neuroimage.2014.01.006>
- Szul, M.J., Papadopoulos, S., Alavizadeh, S., Daligaut, S., Schwartz, D., Mattout, J., Bonaiuto, J.J., 2023. Diverse beta burst waveform motifs characterize movement-related cortical dynamics. *Progress in Neurobiology* 228, 102490. <https://doi.org/10.1016/j.pneurobio.2023.102490>
- Tallon-Baudry, C., Bertrand, O., 1999. Oscillatory gamma activity in humans and its role in object representation. *Trends in Cognitive Sciences* 3, 151–162. [https://doi.org/10.1016/S1364-6613\(99\)01299-1](https://doi.org/10.1016/S1364-6613(99)01299-1)
- Tallon-Baudry, C., Bertrand, O., Delpuech, C., Pernier, J., 1996. Stimulus Specificity of Phase-Locked and Non-Phase-Locked 40 Hz Visual Responses in Human. *J Neurosci* 16, 4240–4249. <https://doi.org/10.1523/JNEUROSCI.16-13-04240.1996>
- Tamila, E., AlHilani, M., Tanaka, N., Tsuboyama, M., Peters, J.M., Grant, P.E., Madsen, J.R., Stufflebeam, S.M., Pearl, P.L., Papadelis, C., 2019. Assessing the localization accuracy and clinical utility of electric and

- magnetic source imaging in children with epilepsy. *Clinical Neurophysiology* 130, 491–504. <https://doi.org/10.1016/j.clinph.2019.01.009>
- Taulu, S., Kajola, M., 2005. Presentation of electromagnetic multichannel data: The signal space separation method. *Journal of Applied Physics* 97, 124905. <https://doi.org/10.1063/1.1935742>
- Taulu, S., Simola, J., 2006. Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements. *Phys. Med. Biol.* 51, 1759. <https://doi.org/10.1088/0031-9155/51/7/008>
- Taulu, S., Simola, J., Kajola, M., 2005. Applications of the signal space separation method. *IEEE Transactions on Signal Processing* 53, 3359–3372. <https://doi.org/10.1109/TSP.2005.853302>
- Taylor, M.J., George, N., Ducorps, A., 2001. Magnetoencephalographic evidence of early processing of direction of gaze in humans. *Neuroscience Letters* 316, 173–177. [https://doi.org/10.1016/S0304-3940\(01\)02378-3](https://doi.org/10.1016/S0304-3940(01)02378-3)
- Ter-Pogossian, M.M., Phelps, M.E., Hoffman, E.J., Mullani, N.A., 1975. A positron-emission transaxial tomograph for nuclear imaging (PETT). *Radiology* 114, 89–98. <https://doi.org/10.1148/114.1.89>
- Tewarie, P., Liuzzi, L., O'Neill, G.C., Quinn, A.J., Griffa, A., Woolrich, M.W., Stam, C.J., Hillebrand, A., Brookes, M.J., 2019. Tracking dynamic brain networks using high temporal resolution MEG measures of functional connectivity. *NeuroImage* 200, 38–50. <https://doi.org/10.1016/j.neuroimage.2019.06.006>
- Tierney, T.M., Alexander, N., Mellor, S., Holmes, N., Seymour, R., O'Neill, G.C., Maguire, E.A., Barnes, G.R., 2021. Modelling optically pumped magnetometer interference in MEG as a spatially homogeneous magnetic field. *Neuroimage* 244, 118484. <https://doi.org/10.1016/j.neuroimage.2021.118484>
- Tierney, T.M., Holmes, N., Mellor, S., López, J.D., Roberts, G., Hill, R.M., Boto, E., Leggett, J., Shah, V., Brookes, M.J., Bowtell, R., Barnes, G.R., 2019. Optically pumped magnetometers: From quantum origins to multi-channel magnetoencephalography. *NeuroImage* 199, 598–608. <https://doi.org/10.1016/j.neuroimage.2019.05.063>
- Tierney, T.M., Holmes, N., Meyer, S.S., Boto, E., Roberts, G., Leggett, J., Buck, S., Duque-Muñoz, L., Litvak, V., Bestmann, S., Baldeweg, T., Bowtell, R., Brookes, M.J., Barnes, G.R., 2018. Cognitive neuroscience using wearable magnetometer arrays: Non-invasive assessment of language function. *NeuroImage* 181, 513–520. <https://doi.org/10.1016/j.neuroimage.2018.07.035>

- Tierney, T.M., Mellor, S., O'Neill, G.C., Holmes, N., Boto, E., Roberts, G., Hill, R.M., Leggett, J., Bowtell, R., Brookes, M.J., Barnes, G.R., 2020. Pragmatic spatial sampling for wearable MEG arrays. *Sci Rep* 10, 21609. <https://doi.org/10.1038/s41598-020-77589-8>
- Tierney, T.M., Mellor, S., O'Neill, G.C., Timms, R.C., Barnes, G.R., 2022. Spherical harmonic based noise rejection and neuronal sampling with multi-axis OPMs. *NeuroImage* 258, 119338. <https://doi.org/10.1016/j.neuroimage.2022.119338>
- Tierney, T.M., Seedat, Z., St Pier, K., Mellor, S., Barnes, G.R., 2024. Adaptive multipole models of optically pumped magnetometer data. *Human Brain Mapping* 45, e26596. <https://doi.org/10.1002/hbm.26596>
- Tsai, L.L., Mair, R.W., Rosen, M.S., Patz, S., Walsworth, R.L., 2008. An open-access, very-low-field MRI system for posture-dependent ³He human lung imaging. *Journal of Magnetic Resonance* 193, 274–285. <https://doi.org/10.1016/j.jmr.2008.05.016>
- Turner, R., 1993. Gradient coil design: A review of methods. *Magnetic Resonance Imaging* 11, 903–920. [https://doi.org/10.1016/0730-725X\(93\)90209-V](https://doi.org/10.1016/0730-725X(93)90209-V)
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *NeuroImage* 15, 273–289. <https://doi.org/10.1006/nimg.2001.0978>
- van Ede, F., Quinn, A.J., Woolrich, M.W., Nobre, A.C., 2018. Neural Oscillations: Sustained Rhythms or Transient Burst-Events? *Trends Neurosci* 41, 415–417. <https://doi.org/10.1016/j.tins.2018.04.004>
- Van Veen, B.D., Buckley, K.M., 1988. Beamforming: a versatile approach to spatial filtering. *IEEE ASSP Magazine* 5, 4–24. <https://doi.org/10.1109/53.665>
- Van Veen, B.D., Van Drongelen, W., Yuchtman, M., Suzuki, A., 1997. Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on Biomedical Engineering* 44, 867–880. <https://doi.org/10.1109/10.623056>
- Vidaurre, D., Hunt, L.T., Quinn, A.J., Hunt, B.A.E., Brookes, M.J., Nobre, A.C., Woolrich, M.W., 2018. Spontaneous cortical activity transiently organises into frequency specific phase-coupling networks. *Nat Commun* 9, 2987. <https://doi.org/10.1038/s41467-018-05316-z>
- Vidaurre, D., Quinn, A.J., Baker, A.P., Dupret, D., Tejero-Cantero, A., Woolrich, M.W., 2016. Spectrally resolved fast transient brain states in

- electrophysiological data. *NeuroImage* 126, 81–95. <https://doi.org/10.1016/j.neuroimage.2015.11.047>
- Vrba, J., 2002. Magnetoencephalography: the art of finding a needle in a haystack. *Physica C: Superconductivity* 368, 1–9. [https://doi.org/10.1016/S0921-4534\(01\)01131-5](https://doi.org/10.1016/S0921-4534(01)01131-5)
- Vrba, J., 2000. Multichannel SQUID Biomagnetic Systems, in: Weinstock, H. (Ed.), *Applications of Superconductivity*. Springer Netherlands, Dordrecht, pp. 61–138. https://doi.org/10.1007/978-94-017-0752-7_2
- Vrba, J., Robinson, S.E., 2001. Signal Processing in Magnetoencephalography. *Methods* 25, 249–271. <https://doi.org/10.1006/meth.2001.1238>
- Wagner, J., Martinez-Cancino, R., Delorme, A., Makeig, S., Solis-Escalante, T., Neuper, C., Mueller-Putz, G., 2019. High-density EEG mobile brain/body imaging data recorded during a challenging auditory gait pacing task. *Sci Data* 6, 211. <https://doi.org/10.1038/s41597-019-0223-2>
- Walker, T.G., Happer, W., 1997. Spin-exchange optical pumping of noble-gas nuclei. *Rev. Mod. Phys.* 69, 629–642. <https://doi.org/10.1103/RevModPhys.69.629>
- Wang, P., Chen, S., Guo, M., Peng, S., Wang, M., Chen, M., Ma, W., Zhang, R., Su, J., Rong, X., Shi, F., Xu, T., Du, J., 2019. Nanoscale magnetic imaging of ferritins in a single cell. *Sci Adv* 5, eaau8038. <https://doi.org/10.1126/sciadv.aau8038>
- Wang, Y., Jin, G., Tang, J., Zhou, W., Han, B., Zhou, B., Shi, T., 2022. Optimized gas pressure of an Rb vapor cell in a single-beam SERF magnetometer. *Opt. Express*, OE 30, 336–348. <https://doi.org/10.1364/OE.447456>
- Welch, P., 1967. The use of fast Fourier transform for the estimation of power spectra: A method based on time averaging over short, modified periodograms. *IEEE Transactions on Audio and Electroacoustics* 15, 70–73. <https://doi.org/10.1109/TAU.1967.1161901>
- Whitham, E.M., Pope, K.J., Fitzgibbon, S.P., Lewis, T., Clark, C.R., Loveless, S., Broberg, M., Wallace, A., DeLosAngeles, D., Lillie, P., Hardy, A., Fronsco, R., Pulbrook, A., Willoughby, J.O., 2007. Scalp electrical recording during paralysis: quantitative evidence that EEG frequencies above 20 Hz are contaminated by EMG. *Clin Neurophysiol* 118, 1877–1888. <https://doi.org/10.1016/j.clinph.2007.04.027>
- Wodey, E., Tell, D., Rasel, E.M., Schlippert, D., Baur, R., Kissling, U., Kölliker, B., Lorenz, M., Marrer, M., Schläpfer, U., Widmer, M., Ufrecht, C., Stuibler, S., Fierlinger, P., 2020. A scalable high-performance magnetic shield for very long baseline atom interferometry. *Review of Scientific Instruments* 91, 035117. <https://doi.org/10.1063/1.5141340>

- Wolters, C.H., Anwander, A., Tricoche, X., Weinstein, D., Koch, M.A., MacLeod, R.S., 2006. Influence of tissue conductivity anisotropy on EEG/MEG field and return current computation in a realistic head model: a simulation and visualization study using high-resolution finite element modeling. *Neuroimage* 30, 813–826. <https://doi.org/10.1016/j.neuroimage.2005.10.014>
- Woolrich, M.W., Baker, A., Luckhoo, H., Mohseni, H., Barnes, G., Brookes, M., Rezek, I., 2013. Dynamic state allocation for MEG source reconstruction. *NeuroImage* 77, 77–92. <https://doi.org/10.1016/j.neuroimage.2013.03.036>
- Wu, X., Pagel, Z., Malek, B.S., Nguyen, T.H., Zi, F., Scheirer, D.S., Müller, H., 2019. Gravity surveys using a mobile atom interferometer. *Science Advances* 5, eaax0800. <https://doi.org/10.1126/sciadv.aax0800>
- Xia, H., Baranga, A.B.-A., Hoffman, D., Romalis, M.V., 2006. Magnetoencephalography with an atomic magnetometer. *APPL. PHYS. LETT.* 89, 211104. <https://doi.org/10.1063/1.2392722>
- Xie, M., Schneiderman, J.F., Chukharkin, M.L., Kalabukhov, A., Riaz, B., Lundqvist, D., Whitmarsh, S., Hamalainen, M., Jousmaki, V., Oostenveld, R., Winkler, D., 2017. Benchmarking for On-Scalp MEG Sensors. *IEEE Trans Biomed Eng* 64, 1270–1276. <https://doi.org/10.1109/TBME.2016.2599177>
- Yoda, K., 1990. Analytical design method of self-shielded planar coils. *Journal of Applied Physics* 67, 4349–4353. <https://doi.org/10.1063/1.344953>
- Zetter, R., Iivanainen, J., Parkkonen, L., 2019. Optical Co-registration of MRI and On-scalp MEG. *Sci Rep* 9, 5490. <https://doi.org/10.1038/s41598-019-41763-4>
- Zetter, R., Iivanainen, J., Stenroos, M., Parkkonen, L., 2018. Requirements for Coregistration Accuracy in On-Scalp MEG. *Brain Topogr* 31, 931–948. <https://doi.org/10.1007/s10548-018-0656-5>
- Zetter, R., J. Mäkinen, A., Iivanainen, J., Zevenhoven, K.C.J., Ilmoniemi, R.J., Parkkonen, L., 2020. Magnetic field modeling with surface currents. Part II. Implementation and usage of bfieldtools. *Journal of Applied Physics* 128, 063905. <https://doi.org/10.1063/5.0016087>
- Zhang, R., Xiao, W., Ding, Y., Feng, Y., Peng, X., Shen, L., Sun, C., Wu, T., Wu, Y., Yang, Y., Zheng, Z., Zhang, X., Chen, J., Guo, H., 2020. Recording brain activities in unshielded Earth's field with optically pumped atomic magnetometers. *Science Advances* 6, eaba8792. <https://doi.org/10.1126/sciadv.aba8792>
- Zhang, Y., Tavrin, Y., Mück, M., Braginski, A.I., Heiden, C., Hampson, S., Pantev, C., Elbert, T., 1993. Magnetoencephalography using high

- temperature rf SQUIDS. *Brain Topogr* 5, 379–382. <https://doi.org/10.1007/BF01128694>
- Zhao, B., Li, L., Zhang, Y., Tang, J., Liu, Y., Zhai, Y., 2023. Optically Pumped Magnetometers Recent Advances and Applications in Biomagnetism: A Review. *IEEE Sensors Journal* 23, 18949–18962. <https://doi.org/10.1109/JSEN.2023.3297109>
- Zhu, Z., Zumer, J., Lowenthal, M., Padberg, J., Recanzone, G., Krubitzer, L., Nagarajan, S., Disbrow, E., 2009. The relationship between magnetic and electrophysiological responses to complex tactile stimuli. *BMC Neuroscience* 10. <https://doi.org/10.1186/1471-2202-10-4>
- Zich, C., Quinn, A.J., Bonaiuto, J.J., O'Neill, G., Mardell, L.C., Ward, N.S., Bestmann, S., 2023. Spatiotemporal organisation of human sensorimotor beta burst activity. *Elife* 12, e80160. <https://doi.org/10.7554/eLife.80160>
- Zimeo Morais, G.A., Balardin, J.B., Sato, J.R., 2018. fNIRS Optodes' Location Decider (fOLD): a toolbox for probe arrangement guided by brain regions-of-interest. *Sci Rep* 8, 3341. <https://doi.org/10.1038/s41598-018-21716-z>
- Zimmermann, E., Brandenburg, G., Clemens, U., Rongen, H., Halling, H., Krause, H.-J., Hohmann, R., Soltner, H., Lomparski, D., Grünekle, M., Husemann, K.-D., Bousack, H., Braginski, A.I., 1997. HTS-SQUID Magnetometer with Digital Feedback Control for NDE Applications, in: Thompson, D.O., Chimenti, D.E. (Eds.), *Review of Progress in Quantitative Nondestructive Evaluation: Volume 16A*. Springer US, Boston, MA, pp. 2129–2135. https://doi.org/10.1007/978-1-4615-5947-4_278