



**University of
Nottingham**
UK | CHINA | MALAYSIA

Design and fabrication for
next generation
Magnetoencephalography

By

Ryan Hill M.Sci.

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

November 2020

Contents

Contents.....	2
Abstract.....	6
Acknowledgements.....	7
Chapter 1: Introduction	9
1.1 Overall aim of the thesis.....	14
Chapter 2: Magnetoencephalography	18
2.1 Origin of the MEG signal	19
2.1.1 Neurons	19
2.1.1.1 Neuron transmission	21
2.1.1.2 Action potentials.....	22
2.1.1.3 Post-synaptic potentials	23
2.1.2 Measurable neuroelectric effects	27
2.1.2.1 Spontaneous activity	27
2.1.2.2 Evoked responses	28
2.1.2.3 Induced effects	29
2.1.2.4 Functional connectivity.....	30
2.2 Data analysis	31
2.2.1 Forward problem.....	32
2.2.1.1 Single sphere model	35
2.2.1.2 Current dipole.....	37
2.2.2 Inverse problem	39
2.2.2.1 Lead fields	39
2.2.2.2 Beamforming	40
2.3 Data collection: the MEG system	44
2.3.1 Cryogenic MEG system	45
2.3.1 Superconductivity and Cooper pairs	45
2.3.2 Superconducting QUantum Interference Device (SQUID)	47
2.3.2.1 Synthetic Gradiometers.....	50
2.3.3 Magnetically shielded room	51
2.4 Commercial SQUID-based MEG systems	52
2.4.1 Issues with these systems	53
2.5 Alternative MEG technologies.....	53
2.5.1 Nitrogen-vacancy (NV-) centres	55
2.5.2 High-temperature (High-T _C) SQUIDs.....	55
2.5.3 Optically-pumped magnetometers (OPMs)	55
Chapter 3: Optically-Pumped Magnetometers	57
3.1 A brief history of OPMs	58
3.2 The QuSpin OPM	62

3.3 Optical pumping	63
3.3.1 Fine structure	64
3.3.2 Hyperfine structure	65
3.3.3 Zeeman structure	66
3.4 Spin-Exchange Relaxation Free (SERF) regime	70
3.5 Signal equations	72
3.6 QuSpin OPM array	76
Chapter 4: Designing a generic OPM-MEG helmet	79
4.1 Introduction	80
4.2 Simulations	82
4.2.1 Methods	82
4.2.2 Simulation results	86
4.3 Temperature measurements	87
4.3.1 Nylon scanner-cast	88
4.3.2 Bike helmet temperature	91
4.4 Prototype helmet – designing coverage	93
4.5 Co-registration	95
4.6 Experimental validation	98
4.6.1 Methods	98
4.6.2 Results	103
4.7 Discussion	104
Chapter 5: Demonstrating lifespan compliance	106
5.1 Introduction	107
5.2 Methods	108
5.2.1 Maternal touch paradigm	108
5.2.2 An interactive motor paradigm (Robin Hood)	109
5.2.2.1 Dealing with dental braces	111
5.2.3 Naturalistic motor learning (ukulele)	112
5.2.4 Data acquisition	113
5.2.5 Data analysis	114
5.2.6 Other	115
5.3 Results	116
5.3.1 Maternal touch	116
5.3.2 Robin Hood	119
5.3.3 Ukulele	119
5.4 Discussion	121
Chapter 6: Designing a whole-head OPM system	125
6.1 Introduction	126
6.2 Bike helmet 2.0	127

6.3 Helmet design.....	130
6.4 Co-registration	133
6.4.1 Co-registration accuracy.....	136
6.5 Effect of co-registration error in simulation	138
6.5.1 Results	140
6.6 Estimating ‘whole-head’ coverage in simulation	143
6.7 Further considerations in a whole head system	145
6.7.1 Cable management	146
6.7.2 Cable crosstalk.....	147
6.8 Conclusion	151
Chapter 7: Multi-channel whole-head OPM-MEG.....	153
7.1 Introduction.....	154
7.2 OPM-MEG system description.....	155
7.3 Experimental method	159
7.3.1 Paradigm design	160
7.3.2 Data acquisition	160
7.4 MEG data analysis.....	161
7.5 Results	165
7.5.1 MEG data – sensor-space comparison	165
7.5.2 Source-space comparison and summary statistics.....	168
7.6 Discussion	172
7.6.1 Helmet design.....	172
7.6.2 Comparison with existing state-of-the-art	174
7.6.3 Future challenges	178
7.7 Conclusion	180
Appendix 1: Alpha band summary	180
Appendix 2: Subject 2 results.....	183
Chapter 8: A naturalistic motor learning paradigm.....	186
8.1 Introduction.....	187
8.2 Methods	188
8.2.1 OPM-MEG system description	189
8.2.2 Paradigm design	191
8.2.3 Data acquisition.....	191
8.2.4 Data analysis.....	192
8.2.5 Audio analysis.....	193
8.2.6 Motion analysis	197
8.2.7 Left vs. right hemisphere peak location	200
8.2.8 Beta rebound amplitude vs. trial score	201
8.2.9 Functional connectivity	202
8.3 Results	203

8.3.1 Source localisation and reconstruction	203
8.3.2 Left vs. right hemisphere peak location	205
8.3.3 Beta rebound amplitude vs. trial score	206
8.3.4 Functional connectivity	207
<i>8.4 Discussion</i>	212
8.4.1 Technical discussion	212
8.4.2 Neuroscience discussion	214
8.4.3 Issues and future requirements	215
8.5 Conclusion	217
Chapter 9: Concluding remarks	218
9.1: <i>Overview</i>	219
9.1 <i>Future work</i>	221
9.2 <i>Final thoughts</i>	224
References	225

Abstract

Magnetoencephalography (MEG) is a functional neuroimaging technique which, via assessment of magnetic fields generated by neural current, probes human brain function with high spatial and temporal accuracy. Current state-of-the-art MEG systems use Superconducting QUantum Interference Devices (SQUIDs) to detect these magnetic fields, which are roughly a billion times smaller than the Earth's magnetic field. However, these systems are expensive and rely on liquid helium to maintain superconductivity, which imposes significant limitations. The need for a thermally insulating vacuum between the participant's head and the sensors means there is typically a 2-5 cm scalp-to-sensor distance. The sensors are also fixed in place in a one-size-fits-all helmet, and so the gap is inhomogeneous with the largest brain-to-sensor distances typically in frontal areas. This gap increases dramatically for individuals with small heads (e.g. infants). In addition, any movement greater than 5 mm relative to the static sensor array will significantly degrade data quality.

Recently, Optically-Pumped Magnetometers (OPMs) have been demonstrated as potential successors to SQUIDs for use in MEG. They operate at body temperature allowing direct placement on the scalp, both increasing the signal-to-noise ratio and removing movement constraints. The array can be adapted to any head shape and size, and the lack of cryogenics removes the high running costs of the system. These benefits should allow MEG to be more accessible to research and clinical groups around the world, and provide a more wide-scale uptake of MEG as a functional imaging modality.

This thesis aims to develop the first wearable whole-head OPM-MEG system. This system can be deployed across the lifespan, and enable motion robustness so participants can move freely during a scan. Through the design of a generic helmet (and accompanying methods for co-registration), we present a demonstration of our system in young children, teenagers, and adults alike, obtaining high fidelity MEG data in all participants. We present novel paradigms that exploit the motion robustness of a wearable OPM-MEG system, as well as the first demonstration of whole-head coverage, and a comparison to the current state-of-the-art.

Acknowledgements

First I want to say a huge thank you to my supervisors Prof. Matthew Brookes and Prof. Richard Bowtell, for your help and guidance throughout my PhD. I am truly grateful for the opportunity to contribute to this amazing project, and work alongside such a fantastic team.

Second I want to thank the amazing MEG team at Nottingham. You've all become such great friends, and the MEG socials (typically involving curry and beer) are always a brilliant time. To Elena (aka "The Boss"), none of this work would have been possible had you not laid the foundations for us all. You will always be the face of OPM-MEG, whether you like it or not! To "Best Friend Niall", you've been my drinking buddy, conference trip roommate, and basically my big brother throughout the PhD. Without your nulling work, we would never be able to perform such amazing and exciting paradigms. To Dr. Jim Leggett, for your electronics and LabView expertise, and just generally being the guy to fix everything! To Lukas, thank you for being my tour guide, translator, and drinking buddy (I'm getting a few of those...) in Rome, and jam session buddy. Your work on TBI is amazing, even if your 'subtraction in 7s' paradigm hurts my head. To George, for being a fellow guitar and music geek, and your mental encyclopaedia of all things MEG. It's great to have you on the OPM team down at UCL. To Molly and Natalie, for your enthusiasm and willingness to be a part of everything that happens in the lab. I can't wait to see the direction the two of you take the OPM work.

None of the work in this thesis could have been achieved without the many collaborators we are so privileged to work with. To Dr. Vishal Shah, James Osborne, and the rest of the amazing team at QuSpin, for your continuous support in our research. Your sensors have truly revolutionised MEG. To the MSL team, for your incredible work in MSR design. I am very excited for the future our teams have together. To the team at UCL, for the many years of

collaboration, with many more to come. To Prof. Rebecca Slater and Dr. Caroline Hartley, for your help and expertise in paediatric scanning. Rebecca, I will be forever grateful to both of your sons for their patience and politeness.

I also want to thank the SPMIC community for being such a wonderfully friendly and sociable place to work. Special thanks go to Lesley for being the welcoming smile at reception every day, and to Alan for all the equipment you helped build. I hope you both enjoy your well-deserved retirement.

To Mom and Dad, I would not be where I am today without your never-ending support and enthusiasm for everything I do. To the happiest little Labrador, Maia, you have kept me sane while writing this thesis (Who's a good girl?!). And finally, to Ella. Thank you for always being there at the end of the day, and supporting me through everything. I love it when you read to me, but maybe don't read me this thesis!

Chapter 1: Introduction

A knowledge of brain science will provide one of the major foundations of the new age to come. That knowledge will spawn cures for disease, new machines based on brain function, further insights into our nature and how we know. There is no better ground for hope in things human.

- Dr. Gerald Edelman, 1995

Our understanding of the human brain has progressed dramatically over the last few decades thanks to advances in non-invasive neuroimaging modalities. Such technologies allow us to gain important insights on how the human brain functions across a range of ages, diseases and mental health conditions. These modalities can generally be split into two types of imaging techniques: **structural** and **functional**. Structural imaging techniques, such as X-Ray Computed Tomography (CT) (Hounsfield, 1973) and Magnetic Resonance Imaging (MRI) (Lauterbur, 1973; Mansfield and Grannell, 1973), provide a non-invasive snapshot of brain structure with very high spatial resolution (of the order 1 mm or better). This allows for structural abnormalities (such as lesions, tumours, and intracranial bleeding) to be assessed, but they provide little information on brain function. Assessment of function means gaining an understanding of the complex electro-chemical activity of the 86 billion neurons in the brain.

Function is mediated via passing electrical currents along neurons. Functional imaging techniques either measure these currents directly, or indirectly via the secondary changes in physiology. In imaging laboratories worldwide, both research and clinical, several of these techniques are used regularly, and we describe five of them below (Figure 1.1 shows a summary of the spatial and temporal resolution of all the systems described):

- **Functional Magnetic Resonance Imaging (fMRI)** (Ogawa et al., 1990) relies on the fact that cerebral blood flow and neuronal activation are coupled. When a brain region becomes ‘active’ (i.e. the neurons in that region fire), blood flow in that region increases. This is because the increased neuronal energy demand is supplied by an increase in oxygenated blood. Blood releases oxygen to active neurons at a greater rate than to inactive neurons, causing a change in the relative levels of oxy- and deoxyhemoglobin. This change can be detected based on their difference in magnetic susceptibility. This is known as

Blood-Oxygen-Level-Dependent (BOLD) imaging. This technique, while having a high spatial resolution, is limited in its temporal resolution because the BOLD response is an indirect measure of neuronal activity and changes occur on the order of seconds.

- **Positron Emission Tomography (PET)** (Fox et al., 1984) uses a radioactively labelled isotope (for example, Oxygen-15 or Fluorine-18) with unstable nuclei which decay by positron emission. On (almost instant) collision with an electron, the positron and the electron will mutually annihilate causing two gamma rays to be emitted at $\sim 180^\circ$ to each other. Such an isotope is administered to a patient, and an array of detectors are placed around them. Using back-projection-reconstruction, the location of annihilation can be determined, that, when overlaid onto a structural image typically acquired with a CT scan, can be mapped to a location in the body. By using Oxygen-15, blood flow in the brain can be probed, and active regions identified. This technique is once again limited by its temporal resolution (due to the indirect measure of neuronal currents), but also the use of radiation required to obtain both the structural and functional images prevents repeated use in a single participant.
- **Functional Near-Infrared Spectroscopy (fNIRS)** (Chance et al., 1993) measures the absorption of near infrared light by haemoglobin which changes depending on blood volume, flow, and oxygenation. By measuring the characteristic absorption spectra in the brain, we can obtain an indirect measure of brain function by again inferring activity from changes in blood-oxygen concentration. Unlike fMRI and PET, which are both cumbersome and costly, and require participants to remain still during acquisition, fNIRS consists of a set of optodes mounted

on the head in some form of helmet or cap. This allows it to be much more easily deployed across vulnerable patient cohorts, with extensive use in scanning children. However, the system still suffers from a poor temporal resolution, as well as a poor spatial resolution due to light propagation in scattering media.

- **Electroencephalography (EEG)** (Berger, 1933) measures the changing electric potential on the scalp surface that is generated by synchronised current flow through neurons in active brain regions. The electrical potential is measured using electrodes that are attached to the scalp. This makes EEG similar to fNIRS in practicality as it offers a head mounted measurement. Because it offers a direct measure of the electrical activity, it also has excellent temporal resolution (of the order of milliseconds), but the spatial resolution is severely limited. This is due to the skull's high electrical resistance, which distorts the electric potentials as they pass through the skull before being measured at the scalp.
- **Magnetoencephalography (MEG)** (Cohen, 1968) measures the changes in magnetic field outside the head generated by the same neuronal currents that produce the electric potential measured in EEG. MEG therefore has the same high temporal resolution as EEG. However, the magnetic fields remain relatively undistorted by the skull, and so the spatial resolution is significantly better. Consequently, of the systems described, MEG offers the best combination of spatial and temporal resolution, with direct and non-invasive measures of neuronal current. However, MEG is hindered by its use of superconducting sensors which must be cryogenically cooled. This leads to a cumbersome and expensive system and significant restrictions on the practicality of MEG.

There are currently around 150 cryogenic MEG systems around the world being used in both research and clinical institutions, but there are still many fundamental limitations that prevent wider uptake of MEG as an imaging modality. First, the sensor-to-brain distance is typically 2-5 cm for an adult brain, but is even greater for children. Such a distance dramatically decreases the signal-to-noise ratio in MEG, a significant confound when trying to measure already tiny magnetic fields from the brain in the presence of large external interference sources. Second, the sensors are fixed in place which means that any movement of the participant relative to the sensors degrades the data quality. This leads to an unnatural and impractical scanning environment. Finally, the high purchase and maintenance costs (largely due to the need for liquid helium) limit the accessibility of these systems for both clinical and research institutions.

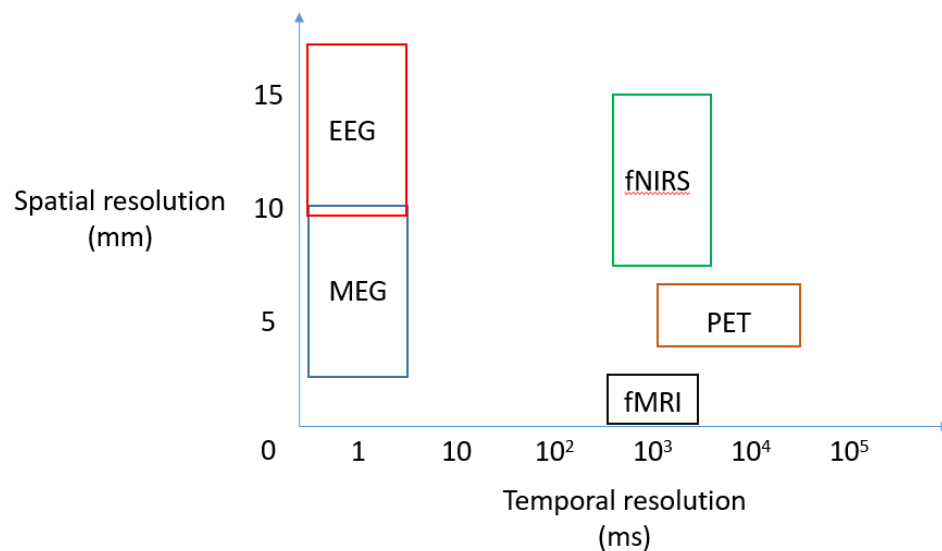


Figure 1.1: Spatial vs. Temporal resolution for functional neuroimaging systems.

In recent years, thanks to commercialisation and miniaturisation, Optically-Pumped Magnetometers (OPMs) have been demonstrated as potential successors to the cryogenic sensors currently used in MEG (Shah and Wakai, 2013). They operate at approximately body temperature which allows them to be placed directly on the scalp, both helping increase the signal-to-noise ratio as well as removing the constraint on movement. The array can be

adapted to any head shape and size, similar to EEG and fNIRS, but maintains its superior temporal and spatial resolution. The lack of cryogenics also removes the high running costs of such a system, potentially making MEG more accessible to research and clinical groups around the world. If OPM-based MEG could be developed to the stage where it can compete with conventional MEG, the combination of the practicality, cost, and high fidelity data could lift the restrictions that surround the current generation of MEG systems.

1.1 Overall aim of the thesis

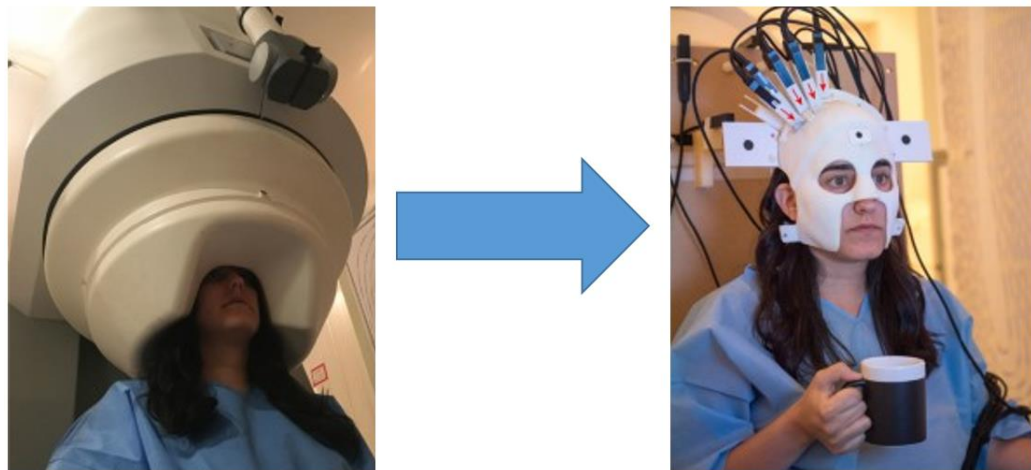


Figure 1.2: Proof-of-principle system. The progress made by Boto et al. 2018 (Boto et al., 2018). The large, restrictive cryogenic system has been reduced to a wearable helmet, although only a small number of sensors can be employed over one region of the brain.

Initial work by Boto et al. (Boto et al., 2018) showed proof-of-principle of OPM-MEG, with high fidelity data captured whilst a participant moved freely (see Figure 1.2). The system used in this study offers great promise for OPM-MEG, but it still has several limitations. First, the system only uses a small number of sensors (13 at maximum) placed over the right motor cortex. While source localisation was performed, it could only ever reconstruct sources in the right motor cortex (i.e. directly beneath the sensors), no matter the quality of the data. Second, the scanner-cast used to hold the sensors rigidly on the scalp is designed such that it can only fit a single participant. While the cost of printing a single helmet is not enormous (~£2000), if a large cohort were to be studied, the cost of the helmets would soon preclude a wide-scale uptake of

MEG. The helmets, coupled with the weight of the sensor cabling, are also heavy and somewhat intimidating, which prevents paediatric populations from being studied (thus removing one of the major benefits to wearable MEG over cryogenic MEG). In addition, the sensor cabling weight prevents practical deployment as a whole-head device.

In this thesis, we aim to design and build the world's first whole-head wearable OPM-MEG system. This will eclipse the current state-of-the-art cryogenic systems by offering greater SNR across the whole brain. We will use a generic design so that multiple head shapes and sizes can be accommodated, offering lifespan compliance to enable a better understanding of brain development. This work will represent the push from a proof-of-principle experimental system to a commercially-viable device that can be utilised by research and clinical groups around the world.

This thesis is divided into the following chapters:

- **Chapter 2** gives an overview of the theory behind MEG. We start from the origin of the MEG signal at the neuronal level, then describe the mathematical models that allow us to analyse MEG data to infer the underlying neuronal currents. We then describe the current state-of-the-art instrumentation for collecting MEG data, followed by a brief overview of alternative technologies.
- **Chapter 3** provides a description of the Optically-Pumped Magnetometer (OPM), starting with a brief history of its development from a table top setup to commercial hand held sensors. We then describe the QuSpin OPM and the physical principles which allow OPMs to sensitively measure magnetic fields.
- **Chapter 4** details the design, simulations, construction of, and pilot experiments for a prototype OPM-MEG system. We start

by assessing potential designs for generic helmet that are suitable and safe for use with paediatric populations. We also devise a new co-registration technique, and perform a finger abduction experiment in three participants to validate the use of a generic helmet to detect, record and localise OPM-MEG signals.

- **Chapter 5** explores the application of the prototype generic OPM-MEG system to multiple age groups. Three separate paradigms are used, all of which elicit beta band modulation, and the difficulty of each paradigm increases with the target age group. We first demonstrate a simple sensory maternal touch task in a 2-, 5-, and 24-year-old participant. Second, we demonstrate a variation on a ballistic finger movement paradigm in a 14-year-old participant, where the participant is prompted by playing a game rather than a standard visual cue. Finally, we show a natural learning paradigm as a 24-year-old participant plays a musical instrument.
- **Chapter 6** builds on our initial experiments to show the design of the first whole-head wearable OPM-MEG system using a second generation of OPMs that are smaller and lighter. We present two methods of holding sensors on the participant's head: a rigid, additively manufactured helmet, and a flexible EEG-style cap. We develop a co-registration procedure for each design, and show how the co-registration errors manifest differently for each. We then assess how these errors affect source reconstruction in simulation.
- **Chapter 7** presents a practical demonstration of the two designs presented in Chapter 6. By using a paradigm that elicits motor-beta and visual-gamma responses, we compare results from the two systems with each other as well as with a state-of-the-art cryogenic system in sensor-space and in source-space

- **Chapter 8** combines the work of the previous four chapters to demonstrate the performance of a 50-channel whole-head OPM-MEG system while performing a naturalistic motor learning paradigm (the musical instrument paradigm from Chapter 5). We assess how beta oscillations are modulated by success in the task, and also perform functional connectivity analysis.
- **Chapter 9** presents concluding remarks and a discussion of the future of OPM-MEG.

Chapter 2: Magnetoencephalography

The functional neuroimaging technique Magnetoencephalography (MEG) measures the weak magnetic field produced by neuronal currents. This chapter outlines the key principles used in MEG. We first look at the origin of neuromagnetic signals in pyramidal neurons in the cortex, where synchronous activity of thousands of these neurons create a measurable magnetic field above the scalp surface. In order to infer the underlying neuronal activity, we describe mathematical methods to interpret and reconstruct the data using forward and inverse modelling solutions. The magnitude of the magnetic fields at the scalp are incredibly small, and so the instrumentation used to detect them must have a high sensitivity. The current state-of-the-art device is the Superconducting QUantum Interference Device (SQUID), and we describe the operation of these devices. However, these devices have significant limitations and so, finally, we discuss briefly some of the emerging technologies that have potential applications in MEG.

2.1 Origin of the MEG signal

The human brain is, perhaps, the most complicated structure in the known universe. Despite being the central organ in our nervous system, brain function, and how it breaks down in mental illness, remains poorly understood. The fundamental units of the brain and nervous system are neurons (nerve cells that carry electrical impulses) and glial cells (which provide both metabolic and functional support to neurons). When electrical currents flow within and between neurons, a magnetic field is produced in accordance with Maxwell's equations. If thousands of neurons act in synchrony, the miniscule fields produced by each individual neuron interfere constructively to allow a small but detectable magnetic field to be measured non-invasively outside the head using highly sensitive magnetic field detectors. The process of measuring these magnetic fields, and interpreting the underlying neural current flow is the basis of Magnetoencephalography (MEG).

2.1.1 Neurons

The neuron is a specialised cell that transmits information within the brain and throughout the body (e.g. controlling muscles). Within the brain's outermost structure (the cortex) there are roughly 100 billion neurons, with each one connected to 10 thousand others. A single neuron contains the following components (shown in Figure. 2.1a):

- **Cell Body (Soma):** Contains the nucleus and the metabolic machinery.
- **Dendrites:** Fibrous roots that branch out from the cell body that receive and integrate signals from other neurons. The soma and the dendrites form the grey matter in the brain.
- **Axon:** A long, slender structure joined to the cell body by a specialised junction called the **axon hillock**. Axons carry information from the neuron to other parts of the brain or body. Many axons are insulated with a fatty substance called **myelin** to help conduct the electrical signal. Axons form

the white matter of the brain, connecting different cortical regions as well as deeper structures.

The distribution of the dendrites around the cell body determines whether a neuron is a **pyramidal** (Figure. 2.1b) or **stellate** (Figure 2.1c) cell. Stellate cells have a mostly symmetric dendritic configuration, and so any electromagnetic field from their dendritic currents cancel, meaning they are not likely to contribute significantly to the MEG signal. However, pyramidal cells have a highly asymmetric dendritic distribution, with the dendrites mostly oriented perpendicular to the cortical surface. This allows the magnetic fields of a group of pyramidal neurons to constructively superpose, hence pyramidal cells are believed to be the main contributor to the extracranial fields observed by MEG.

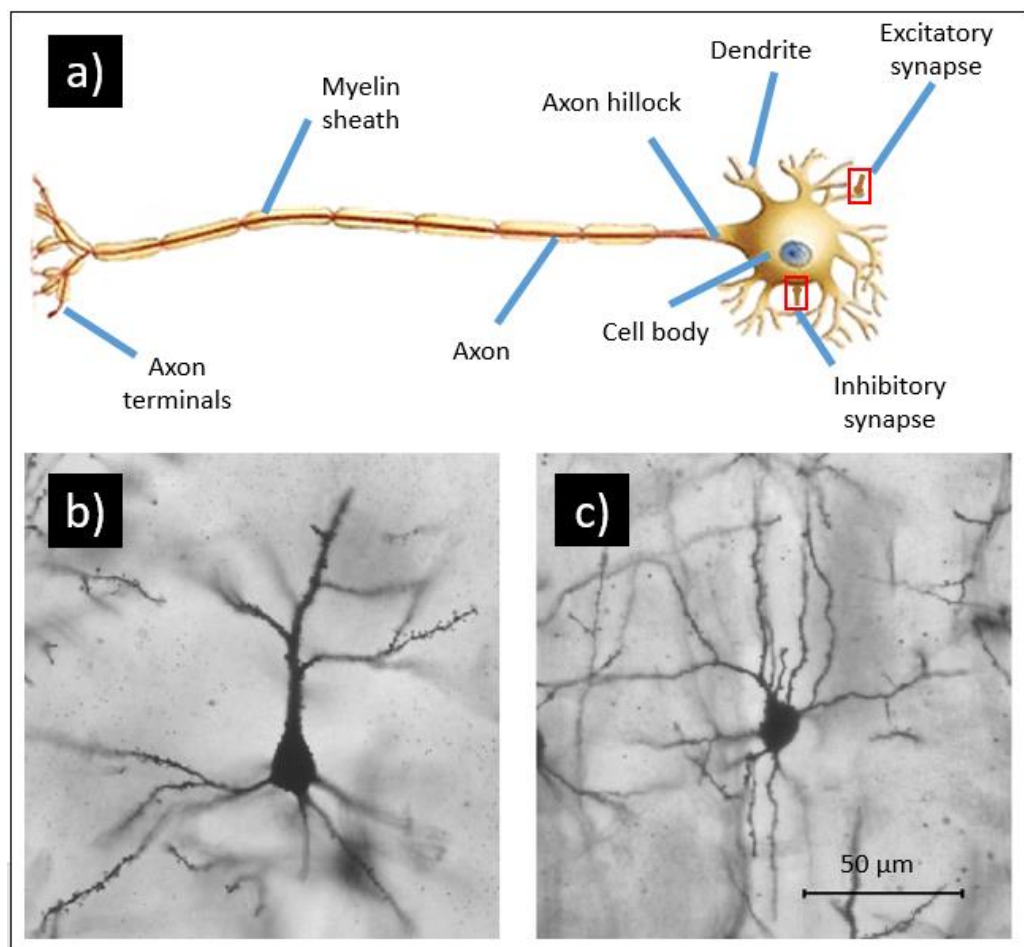


Figure 2.1: The neuron. a) The anatomy of a neuron (adapted from (Lodish et al., 2000)). b-c) Neuronal structure of the asymmetric pyramidal and symmetric stellate cell respectively (adapted from Churchill et al. (Churchill et al., 2004)).

2.1.1.1 Neuron transmission

As with all cells, the neuron is separated into intra- and extracellular regions by an insulating membrane. Each compartment has differing concentrations of ions, mainly potassium (K^+), sodium (Na^+), and chlorine (Cl^-). The extracellular region has a higher concentration of sodium than the intracellular, but a lower concentration of potassium, causing a concentration gradient for each ion across the membrane (where the ions flow in the direction that would balance the gradient). The neuron cell membrane is highly permeable to potassium and so it leaks *out* of the neuron through potassium leakage channels. The membrane is also partially permeable to sodium which can leak *into* the neuron through sodium leakage channels.

In addition to the concentration gradient, an imbalance in ion concentrations also causes a potential difference across the membrane. When the ion exchange is in equilibrium, the potential across the membrane is known as the 'resting state' or 'Nernst' potential. This potential is calculated using

$$V_{Eq.} = \frac{kT}{q} \ln\left(\frac{[X]_{out}}{[X]_{in}}\right), \quad [2.1]$$

where $V_{Eq.}$ is the Nernst potential difference between the intra- and extracellular regions for a given ion, k is the Boltzmann constant, T is the temperature in Kelvin, q is the charge of the ion, and X is the concentration of ions in or out of the cell (denoted by the subscript). However, this equation only considers a single ion species (i.e. either sodium or potassium). In reality, several ion types are present and all contribute to the potential across the membrane. This potential difference is experimentally found to be approximately -70 mV (Goldman, 1943) in the intracellular region relative to the extracellular.

In order to maintain this potential difference, despite the ion leakage, the cell uses an ion pump to move potassium ions back into the cell, and sodium ions out of the cell. However, interactions between cells can alter this potential. If the potential at the axon hillock reaches a threshold level (typically -55 mV), an electrical impulse that propagates along the axon is fired by the neuron (Du Bois Reymond, 1843).

2.1.1.2 Action potentials

Once the potential at the axon hillock reaches -55 mV, the voltage-gated sodium channels in the axon closest to the cell body activate. This allows sodium ions to flow into the axon, depolarising the cell further until it reaches +40 mV within 1-2 ms. The surge in potential difference (the **action potential**) has the ability to depolarise the adjacent region, causing similar effects further down the axon with unattenuated amplitude in a domino-like effect. At +40 mV, inactivation of the voltage-gated sodium channels occurs and the voltage-gated potassium channels opens. The high concentration of potassium ions inside the cell disperses out of the channels reducing the number of positively charged ions in the cell, thus repolarising the neuron and bringing it back towards resting state. The cell enters a brief hyperpolarisation period before the potassium channels close, and the sodium-potassium ion pump re-establishes ion flow equilibrium (resting state). The overall effect is that the action potential is characterised as a leading edge of depolarisation and a trailing edge of repolarisation as it travels down the axon.

The propagation of action potentials down an axon can be thought of as two opposing current dipoles separated by a small distance, allowing them to be modelled as a current quadrupole (Hämäläinen et al., 1993). The magnetic field associated with a quadrupole falls with the cube of the distance, so the fields produced by an action potential are very small at a distance (e.g. the scalp surface). However, if 10,000-50,000 pyramidal cells fire in unison, this signal could theoretically be detected, but the short lifetimes of the action

potentials (1-2 ms) means the probability of synchrony on such a large scale is very low. Because of this, action potentials are unlikely to be the dominant contributors to the MEG signal.

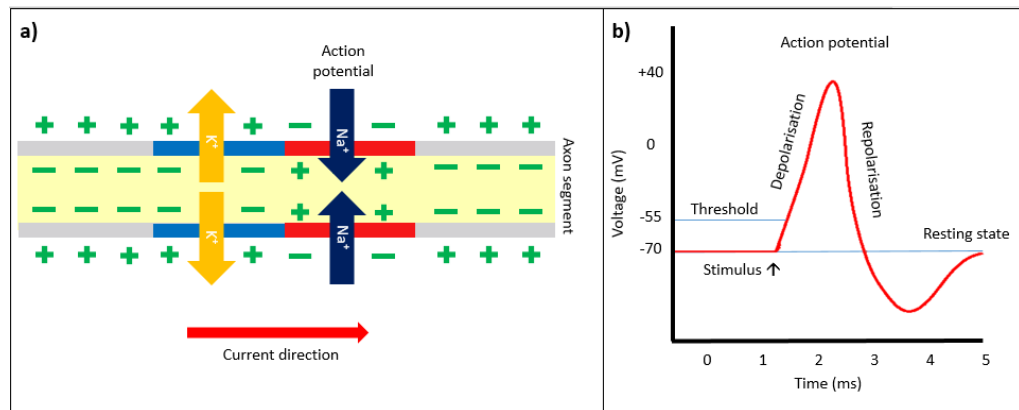


Figure 2.2: The action potential. a) The propagation of an action potential through the neuron. Sodium channels open to depolarise the cell, and potassium channels restore the resting state. The sodium influx makes the region more positive and creates a dipole in the direction of current flow, while the potassium flow out of the cell makes the region more negative creating a dipole in the opposite direction. The influx of positive charge disperses to neighbouring regions in the axon, causing the action potential to propagate down the nerve. b) The characterised increase in potential difference during depolarisation due to opening ion channels.

2.1.1.3 Post-synaptic potentials

As noted above, an action potential occurs when the voltage at the axon hillock reaches a threshold value. This voltage is modulated by electrochemical processes which are initiated in the connections (synapses) between neurons. These processes can either increase (excitatory) or decrease (inhibitory) the intracellular potential. Excitatory synapses are typically located on the dendrites, whereas the inhibitory synapses are typically attached to the cell body (see Figure. 2.3). When an action potential arrives at the end the pre-synaptic neuron axon, neurotransmitter molecules are released into the space between the pre-synaptic axon and the post-synaptic dendrite/cell body (synaptic cleft). These molecules bind to ligand-gated ion channels on the post-synaptic cell, causing them to open and allow ions to flow into the cell, thereby changing the potential difference across the membrane. An excitatory synapse allows the pumping of sodium and potassium ions and increases the intracellular potential (known as an excitatory post-synaptic potential (EPSP)), while an inhibitory synapse allows the pumping of chlorine which decreases the intracellular potential (inhibitory post-synaptic potential (IPSP)). If the sum

of the EPSPs and IPSPs reaches the critical threshold (-55 mV), then an action potential will fire. Therefore, a single excitatory event will not trigger an action potential; multiple events across the neuron are needed. In this way, the neuron itself acts to integrate the excitatory and inhibitory inputs coming from other cells.

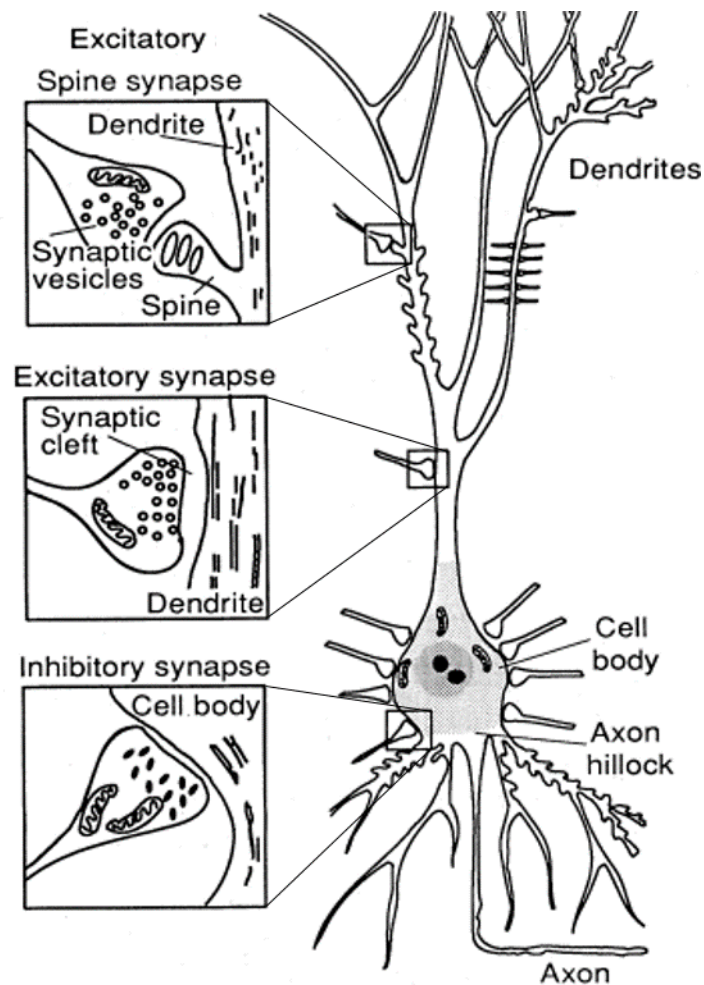


Figure 2.3: Synapses on a pyramidal cell. A schematic representation of the synapse locations on a pyramidal neuron. Excitatory synapses are located on the dendrites (or spines on the dendrites), and inhibitory synapses are located on the cell body. Adapted from Hämäläinen et al. (Hämäläinen et al., 1993).

These post synaptic events create intracellular currents which flow across the synaptic junctions, along the dendrites, and into the cell body. This is referred to as the **dendritic** or **primary current**. Unlike the quadrupole nature of the action potential, post-synaptic potentials (PSPs) are dipolar and their associated magnetic fields decay with the square of the distance, with lifetimes

of roughly 10 ms. This means the magnetic fields associated with PSPs at the surface of the head are stronger than those of action potentials, and the longer lifetime allows a much higher probability of synchrony.

The strength of a post-synaptic current can be calculated using experimental measures of neuronal properties. The strength of a current source, i , decays exponentially with distance x such that

$$i(x) \propto \exp\left(-\frac{x}{\lambda}\right), \quad [2.2]$$

where $\lambda = (\sigma_m \rho_f)^{0.5}$ with σ_m as the conductance of the cell membrane, and ρ_f the resistance per unit length of the intracellular fluid. For a cortical neuron, $\lambda \approx 0.1 - 0.2$ mm (Scott, 1977). The post-synaptic current (if modelled as a current dipole) can be approximated by

$$Q_{PSP} = I\lambda. \quad [2.3]$$

We can also use the change in voltage, ΔV , to estimate the average post-synaptic current as

$$I = \frac{\Delta V}{\lambda \rho_f}. \quad [2.4]$$

This allows us to rewrite equation 2.3 as

$$Q_{PSP} = \frac{\pi d^2 \sigma_f \Delta V}{4}, \quad [2.5]$$

where we have used d as the diameter of the dendrite, and σ_f is the conductivity of intracellular fluid. By inserting typical values ($d = 1 \mu\text{m}$, $\sigma_f = 1 \Omega^{-1}\text{m}^{-1}$, $\Delta V = 25 \text{ mV}$), we find that for a single post-synaptic potential,

$Q_{PSP} = 20 \text{ fAm}$. Hence the MEG signal is most likely to be due to the synchrony of tens of thousands post-synaptic currents in pyramidal neurons.

As with the axon, the resting potential of the cell body must be restored after the primary current by using ion pumps to expel ions back into the extracellular space. This process generates an electric field between the ion expulsion points and the synaptic junction, causing an extracellular or **volume current** in the opposite direction to the primary current (see Figure 2.4). It will be shown later that these currents have little effect on the measurable magnetic field.

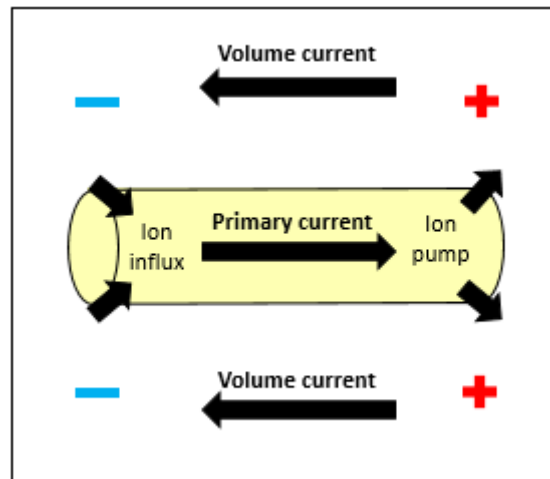


Figure 2.4: Post synaptic potential along a dendrite. The primary current is due to the influx of ions after neurotransmitters are detected at a synaptic junction. The volume current is due to the electric field generated when ions are expelled.

In summary, an action potential occurs in the axon of a neuron, has a short lifetime of 1-2 ms, and the quadrupole nature means the magnetic field falls off with the cube of the distance. The post-synaptic potential occurs in the dendrites (of which there are many on a single neuron) and in the soma, has a longer lifetime of around 10 ms, and has a dipole nature which falls off with the square of the distance. For these reasons, it is believed that primary post-synaptic currents in the dendrites of pyramidal cells are the largest contributors to the MEG signal. However, synchronised populations of action potentials may contribute to very high frequency magnetic fields (>600 Hz) (Curio et al., 1994;

Hashimoto et al., 1996). This was detected outside the pig brain by (Ikeda et al., 2002) using peripheral electrical stimulation.

2.1.2 Measurable neuroelectric effects

The neuromagnetic effects that are detectable by a MEG system are rich in temporal, spectral and spatial information, but the type of information we can extract is highly dependent on the type of recordings we make, and the way in which these signals are analysed. MEG-detectable effects can roughly be divided into three categories: **spontaneous activity**, **evoked responses**, and **induced effects**.

2.1.2.1 Spontaneous activity

Spontaneous activity was first discovered by Hans Berger in humans in 1929 using EEG (Berger, 1933) (Figure 2.5). His work built on prior work in animals by Richard Caton, who was using invasive techniques to investigate electric currents in the brain (Caton, 1875). By measuring differences in electrical potential across the scalp surface, Berger found characteristic oscillations in the 8-13 Hz frequency band over the occipital lobe. He also found that the amplitude of these oscillations could be attenuated by visual stimulation. This has led to much work being done in characterising oscillations in the brain and are commonly grouped into several frequency bands (Mandal et al., 2018):

- Delta (<4 Hz): accompanied with deep levels of relaxation and restorative sleep; associated with unconscious tasks of the body.
- Theta (4-8 Hz): mostly linked with sleep and typically occur during deep meditation; also associated with memory, intuition, and learning during wakefulness.
- Alpha (8-13 Hz): blocked by visual or somatosensory stimulation; associated with resting state oscillations.

- Beta (13-30 Hz): thought to reflect neural inhibition; often associated with the motor cortex.
- Gamma (>30 Hz): thought to represent active cortical processing; often associated with the visual cortex but generally found in all cortical areas.

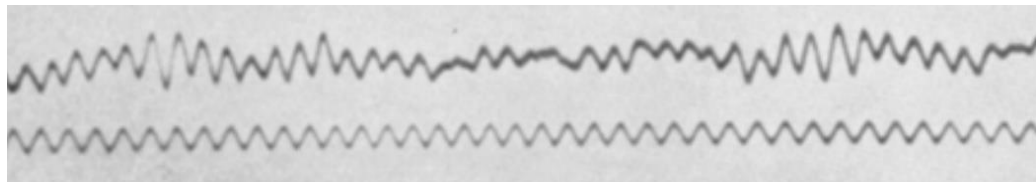


Figure 2.5: Spontaneous alpha activity. (Top) An EEG of the human brain recorded by Hans Berger (Berger, 1933) showing spontaneous alpha activity. (Bottom) A 10-Hz reference signal.

2.1.2.2 Evoked responses

Evoked response signals are time- and phase-locked to an external event. This external event is usually presentation of a stimulus, e.g. in the visual (Alfhors et al., 1992), somatosensory (Hari et al., 1990), or auditory cortices (Mäkelä and Hari, 1990). Experiments that look at evoked responses almost always involve multiple repetitions of a stimulus so that individual trials can be averaged. The phase-locked nature of the evoked response means that the magnitude and morphology of the signal doesn't change from trial to trial. However, non-phase-locked signals (i.e. spontaneous effects, external interference, or sensor noise) will be reduced in amplitude by a factor equal to the square root of the number of trials. Therefore, by averaging trials together, effects of no interest will be attenuated allowing the unchanged evoked response to become more prominent (see Figure 2.6).

These responses can be elicited by many types of stimulus, such as visual, auditory, or tactile (Figure 2.6 shows the evoked response in the somatosensory cortex due to stimulation of the median nerve). The evoked response shows a characteristic pattern of waveform peaks, and these peaks

are altered in certain conditions (for example, multiple sclerosis (Kiiski et al., 2016)).

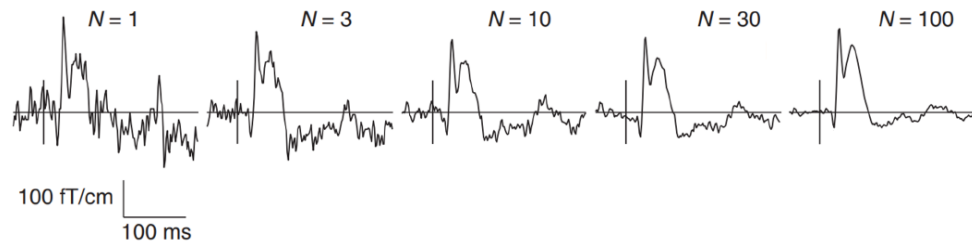


Figure 2.6: Evoked response from median nerve stimulation. The response observed in the somatosensory cortex following electric stimulation of the median nerve. Trials are averaged to reduce effects of noise while preserving the characteristics of the response. Figure adapted from Hansen et al. (Hansen et al., 2010).

2.1.2.3 Induced effects

As with the original experiments by Berger, it has been shown that the amplitude of spontaneous activity in each frequency band can be modulated by both simple sensory and cognitive tasks (Lopes da Silva, 2013; Pfurtscheller and Lopes da Silva, 1999). The stimulus-related change in spontaneous activity is referred to as an ‘induced effect’. Induced effects are time-locked to the stimulus but are not phase-locked meaning they cannot simply be averaged like evoked responses. Instead, the neuromagnetic signals are frequency filtered to the band of interest, and the amplitude envelope is calculated. By averaging the envelopes across trials, the induced effects can be observed.

Modulation of the amplitude envelope is likely to be achieved through a combination of neurotransmitters and **neuromodulators**. Neuromodulators are substances that do not directly activate ion-channel receptors, rather they act together with neurotransmitters to enhance the excitatory or inhibitory responses of the receptors, altering the neuronal ensemble behaviour. One of the most commonly studied effects is the decrease in beta power during voluntary movement, followed by a rebound in amplitude before a return to baseline (see Figure 2.7). This type of response is elicited through a very simple

task where the participant performs a finger abduction when prompted. However, the way in which this task modulates the beta activity varies in neurological conditions such as schizophrenia (Robson et al., 2016) and multiple sclerosis (Barratt et al., 2017), and even by the time of day (Wilson et al., 2014). We can explore how neural oscillations in other frequency bands modulate using alternative tasks. For example, theta oscillations are modulated during navigation (de Araújo et al., 2002) and episodic working memory (Burgess and Gruzelier, 1997) tasks.

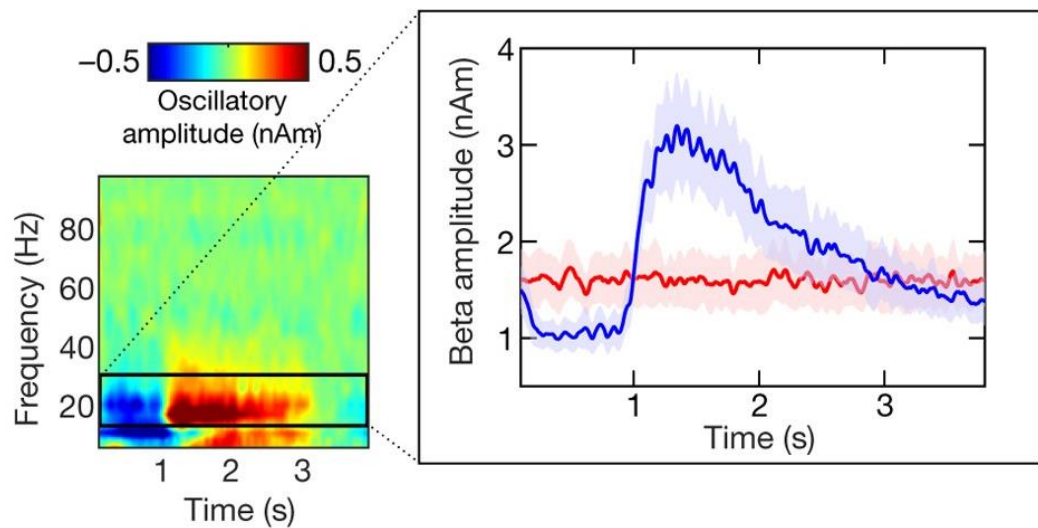


Figure 2.7: Induced response from a finger abduction task. A time–frequency spectrogram (TFS) depicts changes in neural oscillations during finger abduction. The inset graph shows the characteristic beta band response for finger abduction (blue) and rest trials (red). The oscillatory amplitude of the beta band decreases during finger movement (0–1 s), followed by a post-movement beta rebound during rest (1–3 s). Figure taken from Boto et al. (Boto et al., 2018).

2.1.2.4 Functional connectivity

Where we have previously looked at the modulation of the amplitude of neuronal oscillations during tasks, we can also study the phase of these oscillations. In (Fries, 2005), a model that relates neuronal oscillations to long range communication in the brain is proposed. This model suggests that communication is made more likely if the transmitter neurons and the receiver neurons are oscillating coherently with each other, in order to optimally send information. A neuron’s excitability is dependent on the phase of the neuronal oscillation, such that at the peak excitation, spiking of the neuron due to action potentials occurs. It is also at this peak excitation that a neuron is best

positioned to receive electrochemical signals. Therefore, when two regions oscillate in phase, they are more likely to be functionally connected to one another.

Neuronal oscillations do not only occur during task-based paradigms; they are present even in the absence of a task. This allows us to study the functional connectivity of brain regions during both task-based and resting state paradigms. Using MEG, the spatial signatures of these connected regions have been shown by several studies to resemble the networks found by fMRI (Brookes et al., 2011; de Pasquale et al., 2010; Florin and Baillet, 2015). Using this technique, data from multiple studies and participants can be combined to find commonalities in functional networks.

In summary, the high temporal resolution of MEG systems enables us to capture highly dynamic brain signals, with rich features encompassing spontaneous oscillations across a broad frequency range, evoked, and induced responses. Further processing then allows spatiotemporal dynamics to reveal functional networks. As we will see later in this chapter, these effects can be well localised. As a whole, this makes MEG a powerful tool for non-invasive human brain imaging.

2.2 Data analysis

Once MEG data have been recorded, the next step is to use the extracranial magnetic fields to infer the underlying neuronal currents. In order to do this, we need to first model the magnetic field pattern produced by a known current, otherwise known as solving the **Forward Problem**. Once we know this, we can determine the current distribution inside the head from the measured magnetic fields by solving the **Inverse Problem**.

2.2.1 Forward problem

If a current density, $\mathbf{J}(\mathbf{r}')$, is distributed within a volume conductor (for example, the head), the magnetic fields generated can be derived using Maxwell's equations:

$$\begin{aligned}\nabla \cdot \mathbf{E} &= \frac{\rho}{\epsilon} \\ \nabla \cdot \mathbf{B} &= 0 \\ \nabla \times \mathbf{E} &= -\frac{d\mathbf{B}}{dt} \\ \nabla \times \mathbf{B} &= \mu_0 \left(\mathbf{J} + \epsilon \frac{\partial \mathbf{E}}{\partial t} \right),\end{aligned}\tag{2.6}$$

where ϵ is the permittivity of a medium, μ_0 is the permeability of free space, and ρ is the charge density. For almost all biological applications, we can use μ_0 as the permeability of the tissues in the body, since the relative permeability (μ_r) is approximately equal to one. In addition to this, the electromagnetic fields from the brain vary at relatively low frequencies (1-80 Hz) allowing us to adopt a quasistatic approximation (Hämäläinen et al., 1993): this means the time-varying terms in 2.6 can be considered negligible and the last two equations become

$$\begin{aligned}\nabla \times \mathbf{E} &= 0 \\ \nabla \times \mathbf{B} &= \mu_0 \mathbf{J}.\end{aligned}\tag{2.7}$$

The magnetic field outside a volume conductor generated by a current flow within is given by the Ampère-Laplace law:

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_G \mathbf{J}(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dv',\tag{2.8}$$

where $\mathbf{r}$ is the point at which $\mathbf{B}$ is being determined, and $\mathbf{r}'$ is a location inside the volume conductor G . $\mathbf{J}(\mathbf{r}')$ is the total current at location $\mathbf{r}'$. This (as we

have seen in section 2.1.1.3) can be split up into the primary, $\mathbf{J}_P$ (i.e. the current in the dendrite (see Figure 2.4)), and the volume, $\mathbf{J}_V$, currents, so that

$$\mathbf{J}(\mathbf{r}') = \mathbf{J}_P(\mathbf{r}') + \mathbf{J}_V(\mathbf{r}') . \quad [2.9]$$

The volume current results from the effects of the electric field in the extracellular space, and so, in a medium with uniform conductivity σ , it can be written as $\sigma \mathbf{E}$ meaning that,

$$\mathbf{J}(\mathbf{r}') = \mathbf{J}_P(\mathbf{r}') + \sigma \mathbf{E}(\mathbf{r}') = \mathbf{J}_P(\mathbf{r}') - \sigma \nabla V(\mathbf{r}'), \quad [2.10]$$

where $V(\mathbf{r}')$ is the electric potential at $\mathbf{r}'$. By substituting equation 2.10 into 2.8, the magnetic field can be written as

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \left[\int_G \mathbf{J}_P(\mathbf{r}') \times \frac{\mathbf{r}-\mathbf{r}'}{|\mathbf{r}-\mathbf{r}'|^3} dv' - \sum_{j=1}^n \sigma_j \int_{G_j} \nabla V(\mathbf{r}') \times \frac{\mathbf{r}-\mathbf{r}'}{|\mathbf{r}-\mathbf{r}'|^3} dv' \right], [2.11]$$

where the sum in the second term is over different compartments in the head, G_j , with associated conductivities σ_j (see Figure 2.8).

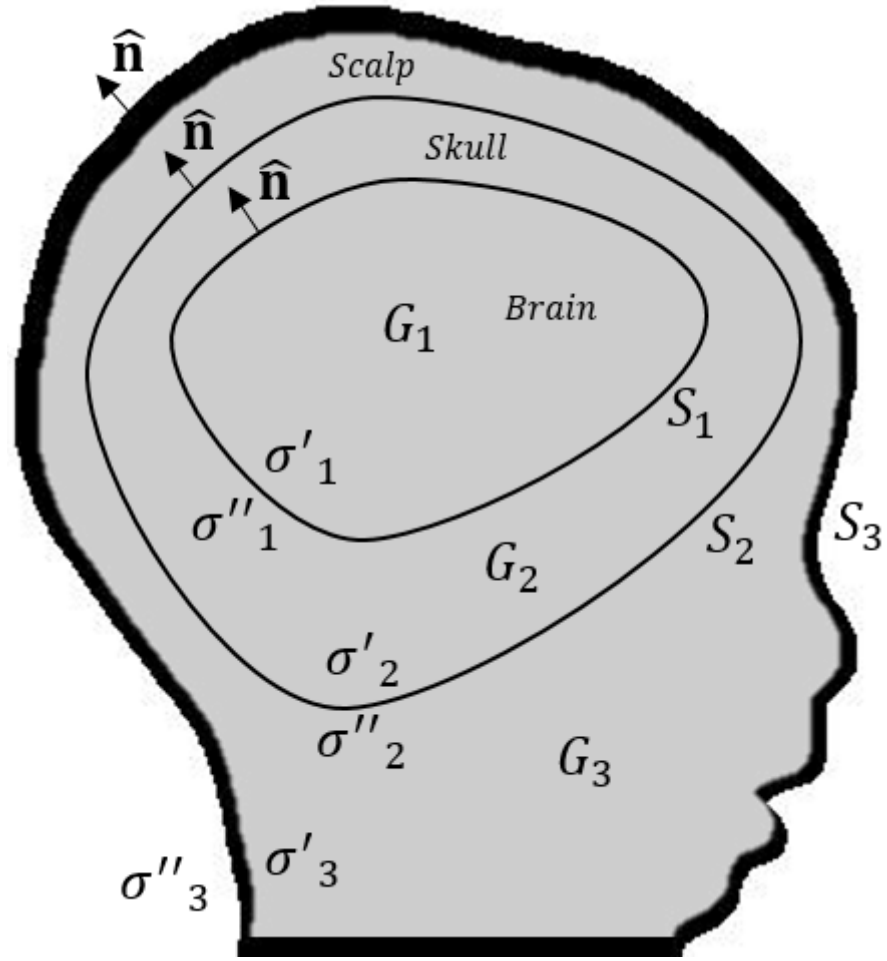


Figure 2.8: Head volumes. Schematic showing three head compartments with volumes G , surfaces S , normal vectors $\hat{\mathbf{n}}$, and conductivities σ .

If we use the vector identity $\nabla a \times \nabla b = \nabla \times (a \nabla b)$, with $a = V(\mathbf{r}')$ and $\nabla b = \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3}$, and apply the generalised Stokes' theorem (which relates a volume integral to a surface integral, i.e. $\int_G \nabla \times \mathbf{X} dv' = \int_S \hat{\mathbf{n}} \times \mathbf{X} dS$), equation 2.11 becomes

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi} \left[\int_G \mathbf{J}_P(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dv' - \sum_{j=1}^n (\sigma'_j - \sigma''_j) \int_{S_j} V(\mathbf{r}') \cdot \hat{\mathbf{n}}(\mathbf{r}') \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} dS_j \right]. \quad [2.12]$$

This is called the Geselowitz formula where σ' and σ'' are the conductivities in adjacent compartments, and $\hat{\mathbf{n}}(\mathbf{r}')$ is a unit vector perpendicular to the surface S_j at point $\mathbf{r}'$. The first term represents the

magnetic fields associated with the primary current and is unaffected by the conductivity of the medium, while the second term represents the fields due to the volume currents.

2.2.1.1 Single sphere model

The human head (including the brain, skull and scalp compartments) can be approximated to a spherically symmetric conductor, with its volume G bounded by a spherical surface S and uniform internal conductivity σ (see Figure 2.9). If we consider the radial component of the magnetic field outside the sphere (which is the component most commonly measured in MEG), we get

$$\mathbf{B}(\mathbf{r}) \cdot \hat{\mathbf{e}}_r = B_r(\mathbf{r}) = \frac{\mu_0}{4\pi} \left[\int_G \mathbf{J}_P(\mathbf{r}') \times \frac{\mathbf{r}-\mathbf{r}'}{|\mathbf{r}-\mathbf{r}'|^3} \cdot \hat{\mathbf{e}}_r dv' - \sigma \int_S V(\mathbf{r}') \cdot \hat{\mathbf{n}}(\mathbf{r}') \times \frac{\mathbf{r}-\mathbf{r}'}{|\mathbf{r}-\mathbf{r}'|^3} \cdot \hat{\mathbf{e}}_r dv' \right]. \quad [2.13]$$

Taking just the second term, we note that

$$\hat{\mathbf{n}}(\mathbf{r}') \times (\mathbf{r} - \mathbf{r}') \cdot \hat{\mathbf{e}}_r = (\hat{\mathbf{n}}(\mathbf{r}') \times \mathbf{r} - \hat{\mathbf{n}}(\mathbf{r}') \times \mathbf{r}') \cdot \hat{\mathbf{e}}_r \quad [2.14]$$

and for a spherically symmetric conductor,

$$\hat{\mathbf{n}}(\mathbf{r}') \times \mathbf{r} \cdot \hat{\mathbf{e}}_r = 0 \quad \text{as} \quad (\hat{\mathbf{n}}(\mathbf{r}') \times \mathbf{r}) \perp \hat{\mathbf{e}}_r \quad [2.15]$$

and

$$\hat{\mathbf{n}}(\mathbf{r}') \times \mathbf{r}' = 0 \quad \text{as} \quad \hat{\mathbf{n}}(\mathbf{r}') \parallel \mathbf{r}'. \quad [2.16]$$

This means that the contribution of volume currents to the magnetic field is reduced to zero for this model, and leaves us with an expression for

$B_r(\mathbf{r})$ that is only affected by primary current and thus is unaffected by the conductivity of the medium:

$$B_r(\mathbf{r}) = \frac{\mu_0}{4\pi} \int_G \mathbf{J}_P(\mathbf{r}') \times \frac{\mathbf{r}-\mathbf{r}'}{|\mathbf{r}-\mathbf{r}'|^3} \cdot \hat{\mathbf{e}}_r dv' . \quad [2.17]$$

This independence on conductivity is attractive because, in practice, very little is known about the conductivity of the human head in vivo.

If we look now at equation 2.17, we see that if the current flow inside the head is radial, then $|\mathbf{J} \times \mathbf{r}'| = |\mathbf{J}||\mathbf{r}'| \sin(\theta) = 0$ as $\mathbf{J}$ is parallel to $\mathbf{r}'$. We also see that $(\mathbf{J} \times \mathbf{r}) \cdot \hat{\mathbf{e}}_r = |\mathbf{J} \times \mathbf{r}| |\hat{\mathbf{e}}_r| \cos(\theta) = 0$ as $\mathbf{J} \times \mathbf{r}$ is perpendicular to $\hat{\mathbf{e}}_r$.

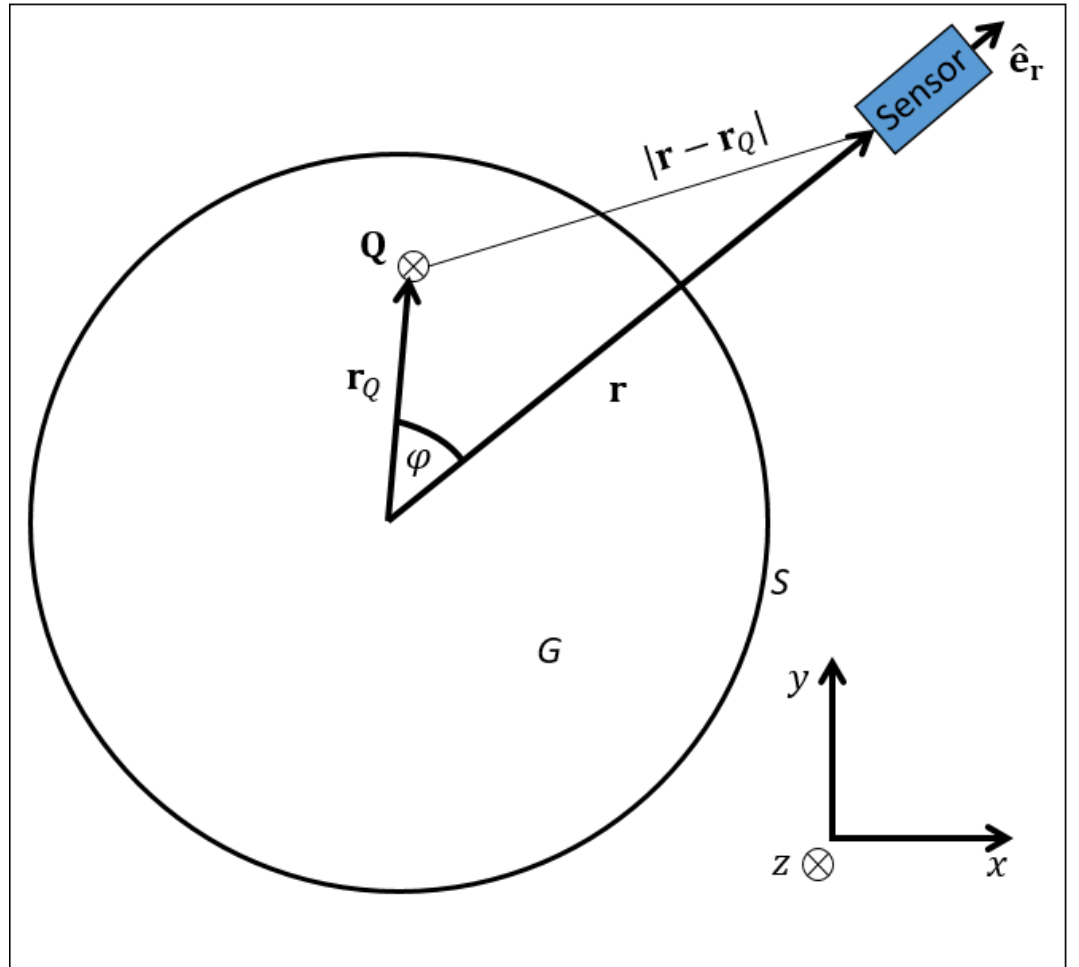


Figure 2.9: The single sphere model. A single sphere with volume G and surface S . A dipole source is located at point $\mathbf{r}_Q$ in the orientated along the z axis. A magnetic field sensor is located at $\mathbf{r}$.

2.2.1.2 Current dipole

To estimate the magnitude of $B_r(\mathbf{r})$, we can approximate the primary current to a current dipole. This allows the primary current density $\mathbf{J}_p(\mathbf{r}')$ to be thought of as a concentration of current at a single point, which can be written mathematically as

$$\mathbf{J}_p(\mathbf{r}') = \mathbf{Q}\delta(\mathbf{r}' - \mathbf{r}_Q), \quad [2.18]$$

where $\mathbf{Q}$ is a current dipole strength, and $\delta(\mathbf{r})$ is the Dirac delta function (defined as $\delta(\mathbf{r}) = \begin{cases} +1, & r = 0 \\ 0, & r \neq 0 \end{cases}$). By substituting 2.18 into 2.17, the expression for $B_r(\mathbf{r})$ can be simplified:

$$\begin{aligned} B_r(\mathbf{r}) &= \frac{\mu_0}{4\pi} \int_G \mathbf{Q}\delta(\mathbf{r}' - \mathbf{r}_Q) \times \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} \cdot \hat{\mathbf{e}}_r dv' = \frac{\mu_0}{4\pi} \frac{\mathbf{Q} \times (\mathbf{r} - \mathbf{r}_Q)}{|\mathbf{r} - \mathbf{r}_Q|^3} \cdot \hat{\mathbf{e}}_r = \\ &= \frac{-\mu_0}{4\pi} \frac{\mathbf{Q} \times (\mathbf{r}_Q)}{|\mathbf{r} - \mathbf{r}_Q|^3} \cdot \hat{\mathbf{e}}_r. \end{aligned} \quad [2.19]$$

This equation gives us a means to calculate the radial component. However, we now need to derive a formula for the total magnetic field outside a spherically symmetric conductor assuming that $\mathbf{J}$ is a current dipole $\mathbf{Q}$ at $\mathbf{r}_Q$ inside G . Outside of G , the total current $\mathbf{J} = 0$ and we can then use $\nabla \times \mathbf{B} = \mu_0 \mathbf{J} = 0$. The magnetic field can then be expressed in terms of a magnetic scalar potential U :

$$\mathbf{B}(\mathbf{r}) = -\mu_0 \nabla U(\mathbf{r}). \quad [2.20]$$

We obtain an expression for U by fixing $\mathbf{r}$ outside G , and by considering a line integral of ∇U along the radius $\mathbf{r} + t\hat{\mathbf{e}}_r$, where $0 \leq t \leq \infty$. As U tends to 0 at ∞ , our expression for U is:

$$U(\mathbf{r}) = - \int_0^\infty \nabla U(\mathbf{r} + t\hat{\mathbf{e}}_r) \cdot \hat{\mathbf{e}}_r dt$$

$$\begin{aligned}
 &= \frac{1}{\mu_0} \int_0^\infty B_r(\mathbf{r} + t\hat{\mathbf{e}}_r) dt = \frac{1}{\mu_0} \int_0^\infty \mathbf{B}_0(\mathbf{r} + t\hat{\mathbf{e}}_r) \cdot \hat{\mathbf{e}}_r dt \\
 &= \frac{1}{4\pi} \mathbf{Q} \times (\mathbf{r} - \mathbf{r}_Q) \cdot \hat{\mathbf{e}}_r \int_0^\infty \frac{dt}{|\mathbf{r} + t\hat{\mathbf{e}}_r - \mathbf{r}_Q|^3}.
 \end{aligned} \tag{2.21}$$

Solving this integral gives:

$$U(\mathbf{r}) = -\frac{1}{4\pi} \frac{\mathbf{Q} \times \mathbf{r}_Q \cdot \mathbf{r}}{F}, \tag{2.22}$$

where $F = a(ar + \mathbf{r}^2 - \mathbf{r}_Q \cdot \mathbf{r})$, $\mathbf{a} = \mathbf{r} - \mathbf{r}_Q$, $a = |\mathbf{a}|$, and $r = |\mathbf{r}|$. By substituting equation 2.22 into 2.20, we get the following expression for the magnetic field outside G :

$$\mathbf{B}(\mathbf{r}) = \frac{\mu_0}{4\pi F^2} (F\mathbf{Q} \times \mathbf{r}_0 - \mathbf{Q} \times \mathbf{r}_0 \cdot \mathbf{r} \nabla F), \tag{2.23}$$

where $\nabla F = (r^{-1}a^2 + a^{-1}\mathbf{a} \cdot \mathbf{r} + 2a + 2r)\mathbf{r} - (a + 2r + a^{-1}\mathbf{a} \cdot \mathbf{r})\mathbf{r}_Q$.

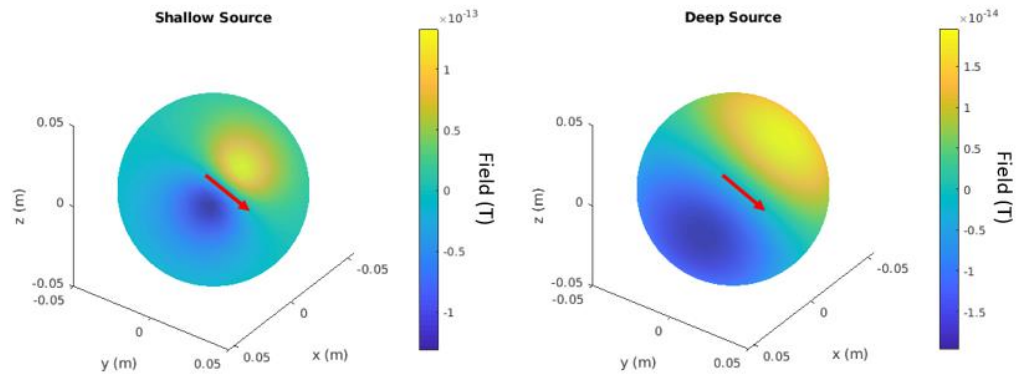


Figure 2.10: Field pattern produced by a current dipole in the spherical model. A current dipole is placed inside a 5-cm radius sphere at a depth of 1.5 mm in the left panel and 3.3 mm in the right. The dipole is tangential to the surface of the sphere. The radial component of the field is shown with yellow representing positive field, and blue representing negative field. Note the difference in colour bar scales.

Figure 2.10 shows the field pattern produced by a shallow (left) and a deep (right) current dipole tangential to the surface using the spherical model (equation 2.23). Using this model, we can see that deeper dipoles are weaker and have a more diffuse field pattern compared to shallower sources. This means that MEG is more sensitive to cortical activity than deep brain activity.

2.2.2 Inverse problem

The forward solution gives us a model of the magnetic fields outside of the head produced by a known current dipole distribution in the brain. For MEG, we need to determine the current distribution given the measured magnetic fields: this is the **Inverse Problem**. The inverse problem is mathematically ill-posed as, because of field cancellation, there are an infinite number of current distributions that can generate the same field pattern. Through the use of optimisation approaches and certain assumptions, this problem can be solved.

2.2.2.1 Lead fields

The lead field results directly from the forward solution and is a key concept for MEG. Suppose that $m_i(t)$ is the magnetic field measured at sensor i in an array of N sensors at time t , we could then write this as

$$m_i(t) = \int_V l_i(\mathbf{r}') \cdot q(\mathbf{r}', t) dv'. \quad [2.24]$$

Here, q is the dipole strength for a location in the brain $\mathbf{r}'$, and $l_i(\mathbf{r}')$ represents a linear mapping of the dipole strength q to the magnetic field m . In other words, l represents a physical model of the fields that we would expect if a dipole at $\mathbf{r}'$ had unit amplitude. This model is termed the **lead field**.

It is standard practice to discretise the brain into a number of voxels, and by assuming that only one dipole exists per voxel (and we know its orientation), we can rewrite the integral in equation 2.24 as

$$m_i(t) = \sum_{j=1}^M l_{i,j} \cdot q_j(t), \quad [2.25]$$

where j is a voxel number; one of a total of M voxels. In matrix form, this can be rewritten as

$$\mathbf{m}(t) = \mathbf{L} \cdot \mathbf{q}(t), \quad [2.26]$$

where $\mathbf{L}$ is the lead-field matrix with dimensions $N \times M$, and $\mathbf{q}(t)$ has dimensions $M \times 1$. The lead-field matrix describes how each dipole maps to each sensor, constructed using the forward model. This equation represents a generative model describing MEG data: in order to solve the inverse problem, we need to invert this equation (i.e. find $\mathbf{q}$ given $\mathbf{m}$ and $\mathbf{L}$). This inversion is not trivial as $\mathbf{L}$ is generally non-square, and there is a linear dependence between rows/columns, so we cannot generate $\mathbf{L}^{-1}$ easily. There are several techniques that can solve this, each with their own assumptions. The source reconstruction results shown in the experimental chapters of this thesis all use a method known as **beamforming**.

2.2.2.2 Beamforming

Beamforming was originally developed for signal processing in radar, geophysical exploration, and communications (Van Veen and Buckley, 1988) but has also been a popular and extensively used solution to the inverse problem in both MEG and EEG (Robinson and Vrba, 1998; Van Veen, 1997). This technique aims to find an estimate of the electrical source strength, $\hat{q}_\theta$ (the ‘hat’ notation is used to represent a beamformer estimate of the actual source strength q_θ), at a given voxel and orientation θ by using a weighted sum of sensor measurements (see Fig. 2.11) such that:

$$\hat{q}_\theta = \mathbf{w}_\theta^T \mathbf{m}(t). \quad [2.27]$$

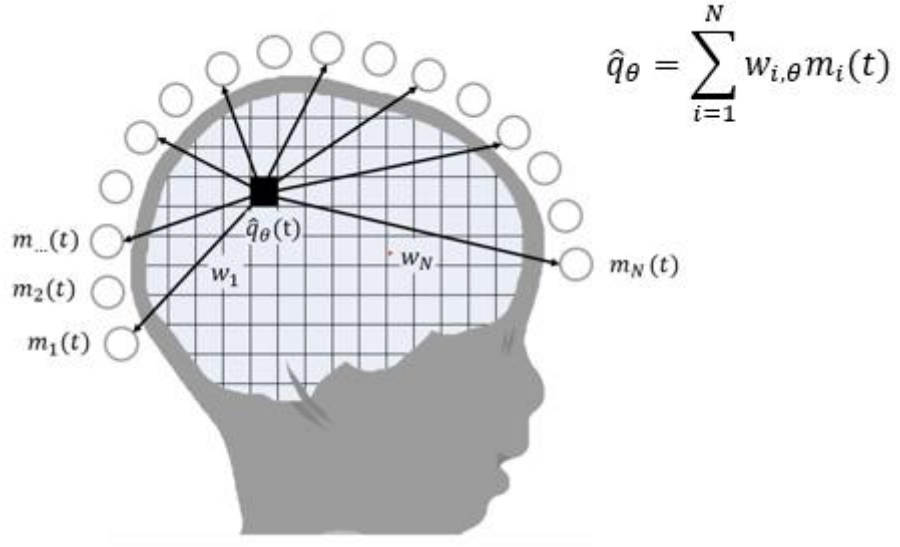


Figure 2.11: The beamforming method. An estimate for the dipole source $\hat{q}_{\theta}$ is found by summing the sensor measurements m_i weighted by w_i .

The beamformer estimate is constructed using the MEG data, $\mathbf{m}$, with the vector of weighting parameters $\mathbf{w}_{\theta}$ tuned to the location and orientation θ . Nearly all source localisation algorithms are formulated in this way with the differences relating to how $\mathbf{w}_{\theta}$ is derived. For beamforming, the coefficients, $\mathbf{w}_{\theta}$, are selected so that the activity at θ is emphasised, while signals from all other locations are attenuated, and this is achieved using variance minimisation: the overall variance in $\hat{q}_{\theta}$ is minimised but with a linear constraint that allows the signals originating from θ to remain. This is mathematically expressed as

$$\min_{\mathbf{w}_{\theta}} |\langle \hat{q}_{\theta}^2(t) \rangle| \text{ subject to } \mathbf{w}_{\theta}^T \mathbf{l}_{\theta} = 1, \quad [2.28]$$

where $\mathbf{l}_{\theta}$ is the forward field for location and orientation θ . Note that $\mathbf{w}_{\theta}^T \mathbf{l}_{\theta} = 1$ due to definition of the lead field model of a unit dipole, so power remains at unity. Using equation 2.27 we see that

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

$$\approx \mathbf{w}_\theta^T \mathbf{C} \mathbf{w}_\theta, \quad [2.29]$$

where $\mathbf{C}$ is an estimate of the covariance matrix of the MEG data (with dimensions $N \times N$), such that the ij^{th} element is the covariance of the data recorded in channels i and j .

Equation 2.28 is solved using a Lagrange multiplier such that

$$\mathbf{w}_\theta^T = \frac{\mathbf{l}_\theta^T \mathbf{C}^{-1}}{\mathbf{l}_\theta^T \mathbf{C}^{-1} \mathbf{l}_\theta}. \quad [2.30]$$

The covariance of the data recorded in channels i and j is calculated by

$$C_{ij} = \frac{1}{P} \sum_{p=1}^P m_i(t_p) m_j(t_p), \quad [2.31]$$

where P is the total number of time points. If $\mathbf{C}$ is singular or close to singular, then regularisation is required to provide a stable inversion in equation 2.30. This is usually a Tikhonov regularised matrix, $\mathbf{C}_r = \mathbf{C} + \mu \mathbf{I}$, where $\mathbf{I}$ is the identity matrix, and μ is a regularisation parameter and is typically a small percentage of the maximum eigenvalue of $\mathbf{C}$.

So far, we have assumed that both the position and orientation of the source are known and represented in θ , but in practice this is not the case. Instead, the orientation of the reconstructed source is determined by the orientation that gives the largest signal-to-noise ratio (SNR) at a given location. As we are using the single sphere model, radial sources do not contribute to the MEG signal, and so the dipole orientation is constrained to remain azimuthal to the spherical surface. The weights for a dipole at location $\mathbf{r}$ are then calculated at each azimuthal angle $0 < \varphi < \pi$. The SNR for each angle is determined using the pseudo-Z-statistic

$$Z_{\mathbf{r},\varphi} = \frac{\mathbf{w}_{\mathbf{r},\varphi}^T \mathbf{C} \mathbf{w}_{\mathbf{r},\varphi}}{\mathbf{w}_{\mathbf{r},\varphi}^T \mathbf{I} \mathbf{w}_{\mathbf{r},\varphi}}, \quad [2.32]$$

where φ is chosen based on the maximum value of $Z_{\mathbf{r},\varphi}$. A Z-score is a measure of how many standard deviations a data point is away from the mean. Here, the pseudo-Z-score is a measure of power compared to the uncorrelated noise power (approximated as an identity matrix). This process is repeated for each voxel in the brain, building up a volumetric image of Z-score values. By overlaying this volumetric image with the anatomical MRI, a map of the brain activity can be produced, showing the regions of the brain which are active during a task.

A second measure is the pseudo-T-statistic. A T-score is similar to a Z-score but is used to contrast an active (a) and background (c) time window by finding the power difference before applying noise normalisation. The pseudo-T-statistic is given by

$$T = \frac{Q_a - Q_c}{2 \times Q_c}, \quad [2.33]$$

where $Q_a = \mathbf{w}^T \mathbf{C}_a \mathbf{w}$ and $Q_c = \mathbf{w}^T \mathbf{C}_c \mathbf{w}$ are the active and control powers respectively. A volumetric image can once again be produced by finding the T-score for each voxel within the brain.

The beamformer method we have described here (known as the Linearly Constrained Minimum Variance (LCMV) beamformer) ensures that the energy originating from the source position remains whilst energy from all other locations in the brain is suppressed. The work in this thesis uses magnetometers which are more susceptible to noise than the gradiometers used in cryogenic systems (described in Chapter 2, Section 3.2), hence the beamformer aids in suppressing this interference. However, the beamformer only relies on the data quality, and the lead field (which is itself based on the

forward solution and hence the volume conductor model, current dipole, and quasi-static approximations). Therefore, if any of these approximations are incorrect, the beamformer will not produce the correct solution. Another limitation of the beamformer is correlated sources. If two separate sources are correlated in time, the lead field vectors for each of the sources will add, and the resulting lead field may not correspond to any single source in the brain. The minimisation process will then cause the vector sum to be rejected as it does not match the lead field expected from that position. However, perfect correlation between two sources is unlikely due to both source and sensor noise.

2.3 Data collection: the MEG system

Neuromagnetic signals are extremely small. Even when thousands of neurons fire in synchrony, the signals are on the order of tens to hundreds of femtotesla. This is around a billion times smaller than the Earth's magnetic field (approximately 50 μT). In addition to the Earth's magnetic field, there are magnetic field contributions from the urban environment (e.g. cars, laboratory equipment, power lines), as well as biomagnetic signals from other parts of the body (e.g. the heart, eye movements, muscle contractions), and even from regions of the brain that are of no interest (known as "brain noise"). To be able to detect the neuromagnetic signal in spite of all the external interference is (quantitatively) analogous to hearing a pin drop at a rock concert. Therefore, to successfully measure neuromagnetic signals, there are two basic technical requirements: 1) an array of magnetic field sensors that are sensitive enough to detect the femtotesla signals; 2) a technique to reduce magnetic interference.

2.3.1 Cryogenic MEG system

The current state-of-the-art sensor for measuring the tiny magnetic fields generated by the brain is the Superconducting QUantum Interference Device (SQUID) with a typical noise floor of $2\text{-}5\text{ fT Hz}^{-1/2}$. SQUIDs were first developed in 1964 (Jaklevic et al., 1964), with the first SQUID MEG measurements performed by Cohen in 1972 (Cohen, 1972). Prior to this, Cohen had used a resistive copper coil with 2 million turns to provide the first recording of neuromagnetic signals in 1968, but this solution was highly impractical (Cohen, 1968). Over the next 20 years, whole-head systems were developed with commercially available devices containing ~ 150 channels being introduced in the late 1990s, and systems with ~ 300 channels appearing around 2000-2005. In the following sections, the fundamental physics of the SQUID is introduced.

2.3.1 Superconductivity and Cooper pairs

In 1911, Dutch physicist Heike Kamerlingh Onnes and his team were studying the properties of matter at very low temperature. They discovered that when mercury is cooled to a temperature below 4.2 K, its electrical resistance dropped to zero. This was the first observation of superconductivity and has since been found to occur in a number of materials when they are cooled to sufficiently low temperatures (known as the **critical temperature** T_c). A material in the superconducting state offers no resistance to electrical current, meaning the current can circulate inside the material with no dissipation of energy. However, there is a maximum supercurrent that can flow which is known as the **critical current**. Above this critical current, the material exhibits normal behaviour.

In order to explain superconductivity, three American researchers (John Bardeen, Leon Cooper, and John Schrieffer) established the **BCS** theory in 1957 (Bardeen et al., 1957). According to this theory, vibrations of the lattice (known

as **phonons**) cause electrons to group into pairs (known as **Cooper pairs**) that can move around the solid without friction. The solid can be thought of as a lattice of positively charged ions surrounded by a cloud of electrons. An electron moving through this lattice causes the ions to move slightly due to the negative charge of the electron. This causes a wake of positive charge in the lattice which then attracts another electron, creating a Cooper pair. The energy of a Cooper pair is very low (of the order 10^{-3} eV) and so can be easily broken up by thermal energy (for example, room temperature energy is around 25×10^{-3} eV), hence why superconductivity usually occurs at very low temperature. Despite electrons being fermions, the total spin of a Cooper pair is integer (therefore is a boson), allowing many Cooper pairs to occupy the same quantum state.

In 1962, Brian Josephson predicted that Cooper pairs could tunnel through a non-superconducting barrier placed in between two superconductors (this set up is known as a **Josephson Junction**, and the tunnelling process is known as the **Josephson Effect**) (Josephson, 1962). Cooper pairs can tunnel across the barrier without any resistance (i.e. a supercurrent flows across the barrier) until the critical current is reached. The critical current depends on the size of the junction, the superconducting material, and the operating temperature. However, once this critical current is exceeded, a potential difference develops across the junction.

The wavefunction describing the Cooper pairs in a superconducting ring has to be continuous around the ring. This condition means the magnetic flux passing through the ring is quantised and can only take values of an integral number of flux quantum $\Phi_0 = 2.07$ Wb. The applied field causes a shielding current I_s that maintains a constant flux $n \cdot \Phi_0$ (where n is an integer) through the ring.

2.3.2 Superconducting QUantum Interference Device (SQUID)

SQUIDs use the Josephson Effect to measure extremely small variations in magnetic flux. They are typically a superconducting ring interrupted by one or more Josephson junctions. For this thesis, we will describe the dc SQUID which uses two Josephson junctions.

If we take a superconducting ring and place it in a magnetic field, a current is induced that is dependent on the applied field. This means the current would offer an indirect measure of the applied magnetic field. Unfortunately, any conventional current measurement would destroy the superconductivity and remove the flux quantisation. If instead we create a Josephson junction, the interference of the wavefunctions that describe the Cooper pairs creates a dynamic, flux-dependent resistance across the ring. We can then feed a constant bias current I_b through the SQUID so that changes in the applied magnetic flux will alter the resistance and cause a change in the average voltage measured over the SQUID (see Figure 2.12a).

The relationship between the flux and the resistance is nonlinear: if the flux is changed by $n\Phi_0$, the resistance remains the same, but any other values of flux changes the resistance according to the voltage-vs-flux function of a SQUID (Figure 2.12b). As this function is periodic, we cannot use it to measure the absolute magnetic field, only its variation with time. In addition, changes larger than half a flux quantum cause ambiguous results. Instead, the SQUIDs used in MEG systems are operated in a flux-locked loop, where a feedback signal is sent to cancel out the effect of the measured signal by artificially generating additional magnetic flux, holding the output of the SQUID constant. The artificial signal is the opposite sign to the measured signal hence it is called **negative feedback**. It is this negative feedback which is the true data output from the SQUID, and allows us to linearly track the true measured signal even for variations larger than the flux quantum.

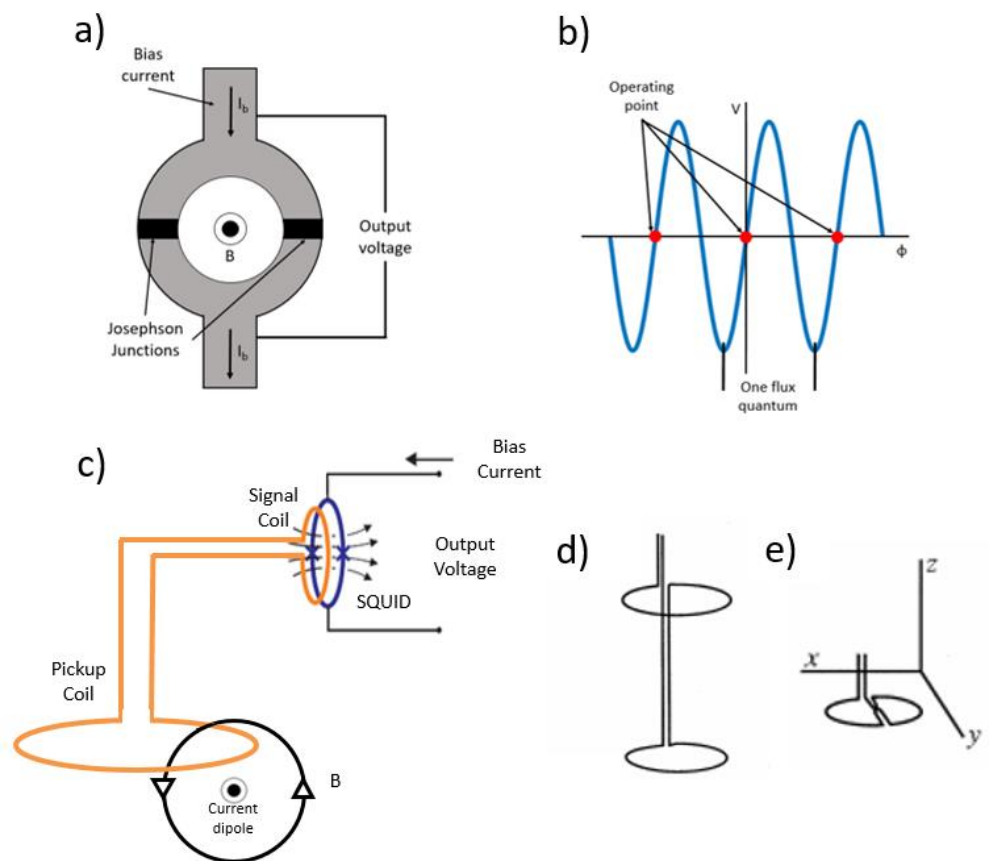


Figure 2.12: DC SQUID. a) DC SQUID schematic. A superconducting ring is interrupted by two Josephson Junctions. If the ring is placed in a magnetic field, a magnetic flux flows inside the ring. This can be measured when a known bias current is applied. b) Voltage-flux function for a constant bias current. In negative feedback, the voltage is held around an operating point to by applying an opposing flux to remove ambiguous measurements. c) A flux transformer (in orange) picks up the field due to neural current and couples it to a SQUID (the blue ring). d-e) Axial and planar gradiometer pickup coil design. Adapted from Hämäläinen et al. (Hämäläinen et al., 1993).

SQUIDS are typically less than 1 mm in outer diameter, and so have poor coupling to the magnetic field. In order to use them in MEG, the coupling of the SQUIDS is enhanced using **flux transformers** (see Figure 2.12c). A flux transformer is also made of superconducting material and serves to collect the magnetic flux from a larger area and concentrate it into the SQUID loop. When in a **magnetometer** configuration, they comprise: a pick-up coil (the closest coil to the scalp), and a signal coil. These coils are typically placed in series so that the net current induced in the pick-up coil circulates through the signal coil, creating a magnetic flux through the SQUID loop.

When in an **axial gradiometer** configuration (see Figure 2.12d), a compensation coil is usually placed around 5 cm above the pick-up coil. The pick-up and compensation coils are wound in opposite directions to each other in order to oppose the currents induced by the magnetic fields. This configuration allows the pick-up coil to detect the magnetic fields originating from the brain, but it will also detect interference fields. However, the compensation coil is placed far enough away from the head to measure the interference fields only. It is assumed that interference fields are from far away sources that manifest as homogenous magnetic fields at neighbouring spatial locations. This means that the interference measured at the compensation coil should be roughly equal to the interference measured at the pick-up coil. This creates a net current due to interference of zero, leaving only the current induced by the magnetic fields from the brain.

A second type of gradiometer configuration is the **planar gradiometer** (see Figure 2.12e). Here, instead of a compensation coil, a second pick-up coil is placed side-by-side with the first pick-up coil in the same plane but again wound in the opposite direction. This configuration is once again insensitive to homogenous fields, but the signal response for a planar gradiometer is at its maximum directly beneath the sensor, whereas axial gradiometer signals peak around the rim of the sensor (Figure 2.13 demonstrates this).

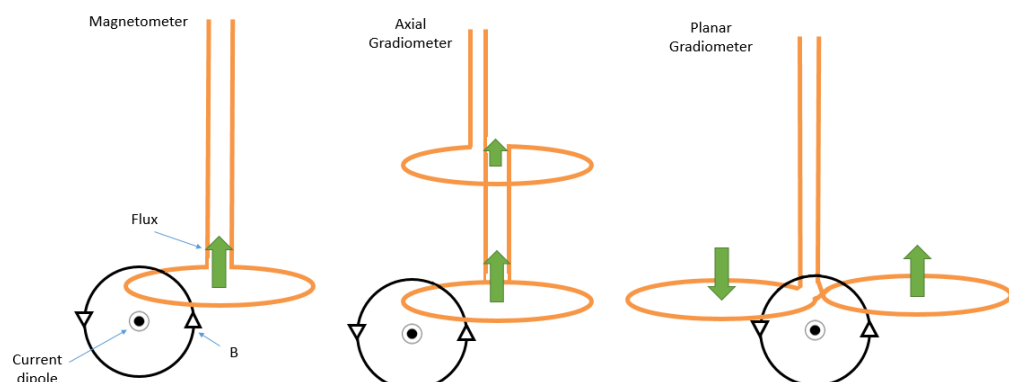


Figure 2.13: Sensitive regions for magnetometer and gradiometer configurations. Magnetometer and axial gradiometer signals peak around the rim of the sensor, whereas the signal response for a planar gradiometer is at its maximum directly beneath the sensor.

2.3.2.1 Synthetic Gradiometers

In addition to the hardwired gradiometers described above, we can also create **synthetic gradiometers** by using a combination of reference sensors placed away from the head (Fife et al., 1999). A first order gradiometer is synthesised using a magnetometer sensor and a vector magnetometer reference. The primary magnetometer sensor measures the magnetic field perpendicular to the coil. The measured field is given by $m_p = \alpha_p (\mathbf{p} \cdot \mathbf{B}_0)$, where α_p is the magnetometer gain, $\mathbf{p}$ is the normal vector of the coil, and $\mathbf{B}_0$ is the magnetic field vector at the centre of the sensor magnetometer. The vector magnetometer reference measures three orthogonal projections of the magnetic field, $\mathbf{B}$, at the centre of the reference magnetometer. If all three coils have the same gain α_r , then the output of the reference is given by $\mathbf{R}_k = \alpha_r \mathbf{B}_k$ where $k = 1, 2, 3$. We can then synthesise a first order gradiometer by projecting the reference output to the vector $\mathbf{p}$ and subtracting it from the magnetometer output:

$$g = m_p - \frac{\alpha_p}{\alpha_r} (\mathbf{p} \cdot \mathbf{R}) = \alpha_p \mathbf{p} \cdot (\mathbf{B}_0 - \mathbf{B}) = \mathbf{p} \mathbf{G} \mathbf{b}_1, \quad [2.34]$$

where $\mathbf{G}$ is the first gradient tensor, and $\mathbf{b}_1$ is the first order gradiometer baseline vector.

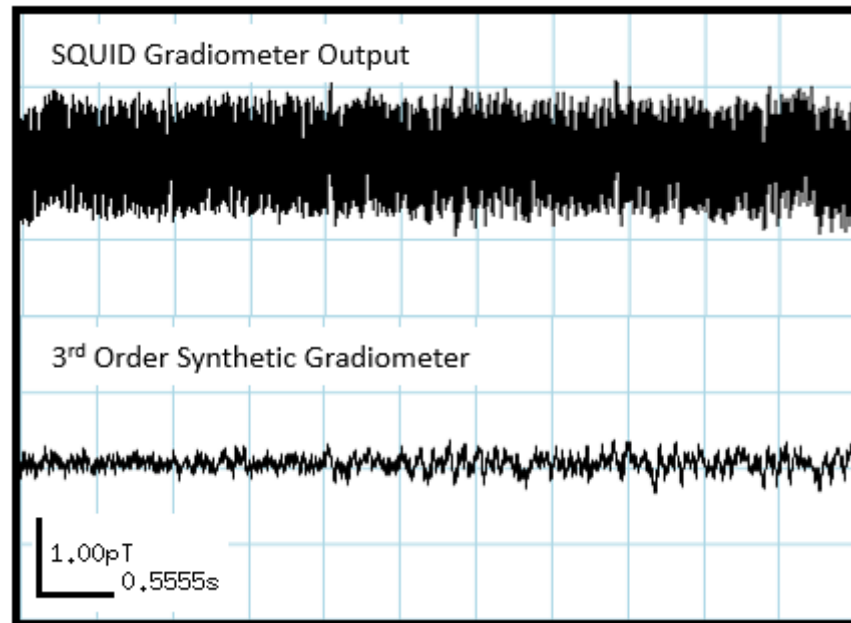


Figure 2.14: Synthetic gradiometer. The effect of a 3rd order synthetic gradiometer on the output of a SQUID gradiometer.

In many commercial systems, synthetic gradiometry is taken to higher orders. For the CTF system at the SPMIC, the dramatic effect of applying a third order synthetic gradiometer is shown in Figure 2.14. By using such a technique, an impressive amount of interference can be removed, but only once the bulk of the environmental interference has been dealt with by a magnetically shielded room.

2.3.3 Magnetically shielded room

As mentioned earlier, in order to detect the minute neuromagnetic fields, we need to reduce as much magnetic interference as possible. Gradiometer configurations offer some noise reduction but only after the bulk of the environmental interference has been reduced. To do this we use a magnetically shielded room (MSR). The most common way to build a MSR is using materials with very high permeability (called μ -metal). Magnetic fields follow the path of highest permeability around the walls of the MSR, and away from the magnetic field detectors. In order to shield from the eddy currents produced by AC sources, layers of conducting metal (usually aluminium) are

placed between the μ -metal sheets. Over the course of my Ph.D., experiments have taken place in two different MSRs. The details of each room are described in the appropriate experimental sections.

2.4 Commercial SQUID-based MEG systems

The current state-of-the-art MEG system uses around 200-300 SQUID-based sensors, contained within a liquid helium (4 K) dewar in order to cool them to their superconducting state. The dewar contains roughly 100 litres of liquid helium and must be refilled periodically as the helium boils off. The participant places their head inside a one-size-fits-all helmet that contains the pick-up coils (see Figure 2.15).

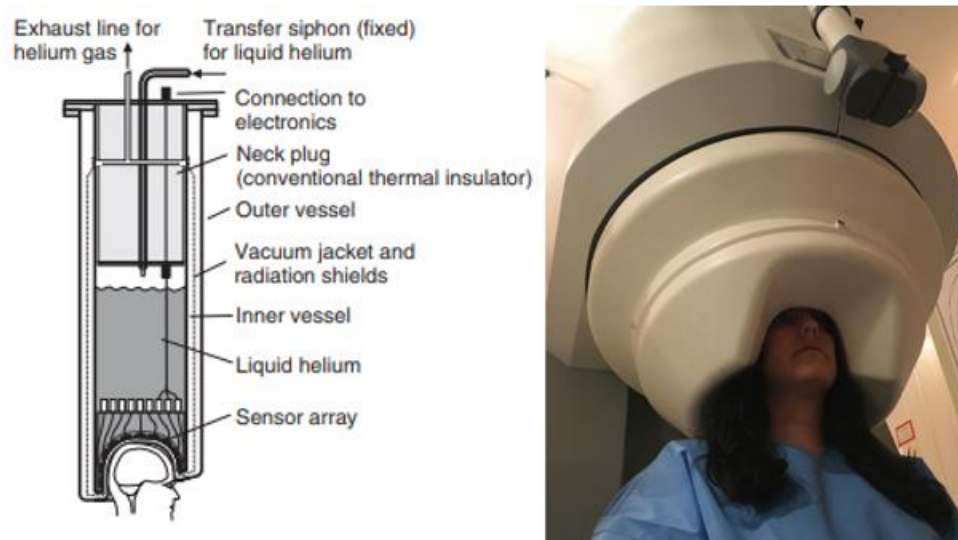


Figure 2.15: Commercial MEG system. The components and layout of a commercial MEG system. Adapted from Hansen et al. (Hansen et al., 2010) and Boto et al. (Boto et al., 2018).

The participant's head is localised inside the helmet using head position indicator (HPI) coils placed on the nasion, and the left and right pre-auricular points. Current is passed through the coils at a known frequency to generate a magnetic field that is detected by the sensors, allowing the location of the coils relative to the sensor array to be determined. A 3D digitiser system (for example, Polhemus (Colchester, Vermont, USA)) is used to record a 3D head

shape for the participant, which includes the locations of the HPI coils. Surface matching of the digitised head shape to a head shape extracted from the participant's MR image allows complete co-registration between brain anatomy and MEG sensor geometry.

2.4.1 Issues with these systems

There are currently around 150 cryogenic MEG systems around the world being used in both research and clinical institutions, but there are still many fundamental limitations that prevent wider uptake of MEG as an imaging modality. The cryogenic dewar means the sensor array is fixed in location inside the one-size-fits-all helmet. There is (at minimum) a 1.5–2 cm gap between the sensors and the head because a thermally insulating vacuum must be maintained between the participant's head and the sensors. This gap is inhomogeneous with the largest brain-to-sensor distances typically in frontal areas because the array can't adapt to different head shapes/sizes. The gap also increases dramatically for individuals with small heads (e.g. infants). Since the MEG signal follows an inverse square law with distance, this means poor signal quality for specific regions (e.g. frontal lobes), or sometimes across the whole brain (e.g. in babies or children). The second major limitation relates to participant movement; any movement relative to the static sensor array will degrade data quality. Even movements of order 5 mm can be problematic and this makes the MEG environment poorly tolerated by many individuals, particularly those with illness inducing involuntary movements such as Tourette's Syndrome or Parkinson's Disease. Finally, the cryogenic infrastructure surrounding a MEG system makes both purchase and running costs high.

2.5 Alternative MEG technologies

Because of the significant limitations associated with cryogenic MEG systems, several new technologies are under development which have the

potential to revolutionise this research area. In an effort to reduce the running costs of cryogenic systems, many are now being fitted with helium recyclers. For example, Elekta MEG systems use a closed-loop zero helium boil-off recycling system which stores and re-liquefies the evaporating helium gas, making the system independent of helium deliveries. But such a system still has issues with fixed sensors, as well as a higher purchase cost and a more complex system. Running costs also remain high due to maintenance contracts on the liquefier.

A far better solution is to create an “on-scalp” MEG systems which can be tailored to fit an individual (see Figure 2.16 for a ‘vision’ of such a system). Such a system would aim to use sensors which do not rely on liquid helium. The SNR of such a magnetic sensor, with similar sensitivity to a SQUID but can be mounted on the scalp, can increase by a factor of 4 relative to a conventional system. In addition improvements in spatial resolution due to sampling of higher spatial frequencies are also possible (Boto et al., 2016; Iivanainen et al., 2017). Three candidate sensors which could be used in such a system are described below: nitrogen-vacancy centres, High- T_c SQUIDs, and optically pumped magnetometers.

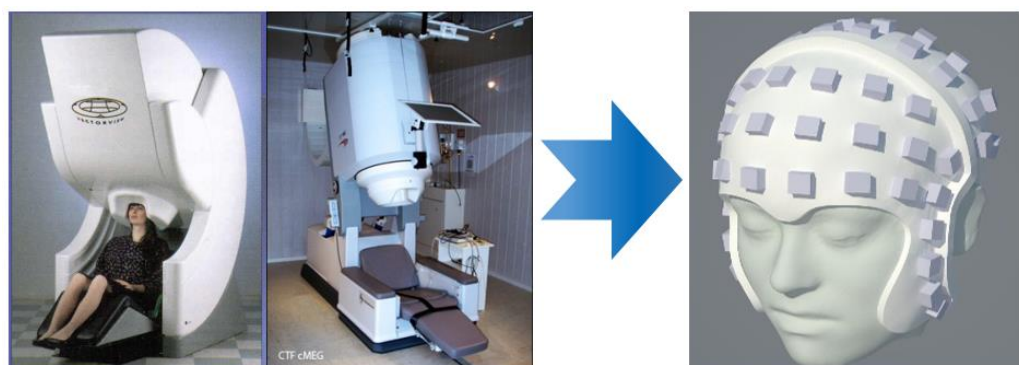


Figure 2.16: The vision. New technologies are aiming to replace expensive, cumbersome cryogenic systems on the left with lightweight, wearable technology as imagined on the right.

2.5.1 Nitrogen-vacancy (NV-) centres

A nitrogen-vacancy (NV-, where ‘-’ denotes a negative charge) centre is a point defect in a diamond crystal lattice and consists of a substitutional nitrogen atom placed next to a missing carbon atom (a vacancy). By using a microwave source and a laser to exploit the electronic spin, the NV- centre can form a magnetically sensitive state with a long coherence time at room temperature (Rondin et al., 2014). Having recently been miniaturised, these sensors could potentially be used in on-scalp MEG, but their sensitivity is currently only a few hundred picotesla which is not yet suitable for detecting neuromagnetic fields (Dale and Morley, 2017).

2.5.2 High-temperature (High-T_C) SQUIDs

The superconducting material used in High-T_C SQUIDs has a higher critical temperature that allows for the SQUID to be cooled using liquid nitrogen (77 K) as opposed to liquid helium (4 K). This allows for less insulation between the sensors and the participant allowing the sensor-to-scalp distance to reduce from several centimetres to less than a millimetre (Andersen et al., 2017; Riaz et al., 2017). Recently, a 7-channel system has been demonstrated with a sensitivity of 50-130 fT Hz^{-1/2} by measuring visual alpha modulation and auditory evoked fields (Pfeiffer et al., 2019). However, because a dewar is still needed to house the sensors and liquid nitrogen, the participant is still unable to move during scanning. The scalp coverage is also limited to ~10 cm² due to the low number of sensors.

2.5.3 Optically-pumped magnetometers (OPMs)

An OPM sensor contains an alkali vapour that is made magnetically sensitive through a process called optical pumping. The vapour is heated in order to achieve suitably long coherence times for magnetometry (150°C for

Rubidium-87) but is insulated so that the external surface of the sensor is approximately body temperature ($<45^{\circ}\text{C}$). OPMs have a sensitivity of $<15 \text{ fT Hz}^{-1/2}$ and a bandwidth of 0-150 Hz which, despite both being lower than SQUIDs, is well suited to MEG (Osborne et al., 2018).

In recent years, OPMs have been used many times for MEG (Borna et al., 2017; Boto et al., 2017; Iivanainen et al., 2019b; Xia et al., 2006) and their lightweight and compact nature allow them to be mounted directly on scalp. This means, with the help of field nulling (Holmes et al., 2018; Holmes et al., 2019), OPMs have been used in naturalistic paradigms in which the participant can move freely during a scan, offering new and exciting possibilities for measuring human brain activity (Boto et al., 2018; Roberts et al., 2019).

Of the above technologies, OPMs currently seem the most promising to realise the wearable MEG system vision. The remainder of this thesis will focus on OPM technology.

Chapter 3: Optically-Pumped Magnetometers

This chapter details a brief history of OPMs, from the production of the first table top sensors to biomagnetic measurements using miniaturised commercial products. An outline of the QuSpin OPM is then provided, followed by the theory of OPM operation with focus on the QuSpin design. Finally, some of the considerations for using a QuSpin OPM array for MEG are discussed.

3.1 A brief history of OPMs

Spin is the amount of angular momentum associated with a particle and was initially characterised in the first half of the twentieth century (Rabi et al., 1938; Stern and Gerlach, 1922; Uhlenbeck and Goudsmit, 1926). By irradiating an atom using light photons (a process known as Optical Pumping), the atomic (both nuclear and electron) spin can be manipulated (Kastler, 1973), and this forms the basis of how OPMs function.

In the late-1950s / early-1960s, the first OPMs were developed by using a light source (e.g. a laser) to cause atomic transitions through absorption and emission of photons, creating a magnetically sensitive system from which the local magnetic field can be measured (Bell and Bloom, 1957; Bloom, 1962). OPMs have been developed with sensitivities comparable to (or even better than) SQUIDs but early systems were bulky, laboratory-based setups (Allred et al., 2002; Dang et al., 2010; Kominis et al., 2003). The first reported MEG measurement using an OPM was an auditory evoked response in Xia et al. (Xia et al., 2006), but the physical size of these initial sensors prevented them from being mounted comfortably on the head. Through significant advances in microfabrication techniques and methods originally developed for chip-scale atomic clocks, OPMs were miniaturised (Schwindt et al., 2007). Despite only having a sensitivity on the order of a few pT, this miniaturisation showed the potential to scale down the size and weight of an OPM to become a viable MEG device. Shah et al. (Shah et al., 2007) improved this sensitivity to a few tens of fT with a table top setup, and further still to less than 10 fT (Shah and Romalis, 2009); this was the generic target for early SQUIDs for use in MEG. By using techniques from manufacturing microelectromechanical systems (MEMS), the magnetometers could be made even more compact into packaged, handheld devices. Some examples of these initial prototype sensors are shown in Figure 3.1.

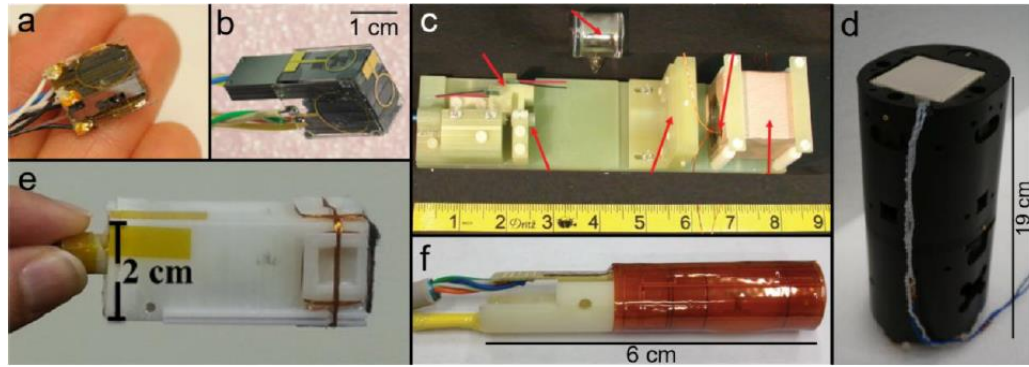


Figure 3.1: Prototype compact OPMs. a) Sander et al., 2012. b) Mhaskar et al., 2012. c) Johnson et al., 2013. d) Kamada et al., 2015. e) Shah and Wakai, 2013. f) Sheng et al., 2017. Taken from Boto (Boto, 2018).

Several groups have provided further demonstration of the MEG capabilities of OPMs. Johnson et al. (Johnson et al., 2010) used a single Spin-Exchange Relaxation Free (SERF) magnetometer to measure the brain's response to median nerve and auditory stimulation, and the same group showed the first MEG measurement using a multi-sensor array to again measure an auditory evoked response (Johnson et al., 2013). Sander et al. (Sander et al., 2012) measured both the somatosensory evoked field as well as occipital alpha modulation during an “eyes open, eyes closed” task using a chip scale OPM (roughly the size of an EEG electrode). A further demonstration of occipital alpha modulation was shown by Kamada et al. (Kamada et al., 2015). A potential clinical application of OPMs was presented by Alem et al. (Alem et al., 2014) where epileptiform activity in rodents was measured. Other biomagnetic signals such as adult and foetal heartbeat have also been measured using OPMs (Batie et al., 2018; Bison et al., 2009; Kamada et al., 2012).

Commercialisation of the OPM sensors allowed them to be produced in larger quantities with more consistency. This allowed an important translation of the technology from the atomic physics groups who develop the sensors to imaging physics groups who wish to exploit them. To date, two companies are providing commercial-grade sensors that are suitable for MEG: QuSpin Inc. (Louisville, Colorado, USA), and FieldLine Inc. (Boulder, Colorado, USA). This

thesis focusses on the QuSpin devices. Boto et al. (Boto et al., 2017) showed that commercially available QuSpin OPMs were able to detect somatosensory evoked fields, as well as modulation of beta oscillations, from median nerve stimulation. However, this was achieved with only a single sensor that was placed in different locations on the head with the experiment repeated multiple times which is not a practical way to study brain function. For OPMs to be used in MEG experimentation, multichannel systems needed to be developed. Borna et al. (Borna et al., 2017) demonstrated a 20-channel system using OPMs developed by the same group to measure auditory and somatosensory evoked fields. A multichannel system using commercial OPMs was later shown in Boto et al. (Boto et al., 2018) using 13 QuSpin manufactured sensors to measure responses in the sensorimotor cortex.

Alongside the development of larger system arrays, methods of holding the sensors close enough to detect biomagnetic signals needed to be developed. Genetesis (a biomagnetic imaging company) developed the “CardioFlux Magnetocardiograph™” system to detect and record magnetic fields from the human heartbeat (called magnetocardiography or MCG) by constructing a cylindrical shield with 36 OPMs placed around the roof of the cylinder. The participant lies with their chest underneath allowing the biomagnetic signal from the heart to be detected. A similar solution was employed by Borna et al. (Borna et al., 2017) but with the sensor array mounted around the participant’s head at the end of the cylindrical shield in order to perform MEG measurements. Iivanainen et al. (Iivanainen et al., 2019b) demonstrate a system that is more similar to a SQUID MEG design by using a static helmet in the centre of a magnetically shielded room, where the sensors could be pushed in until they touched the participant’s scalp. Boto et al. (Boto et al., 2017) took this set up one step further by 3D printing a “sensor cast” based on the participant’s MRI that holds the sensors directly on the scalp. These four examples are shown in Figure 3.2.

Chapter 3: Optically-Pumped Magnetometers

3.1 A brief history of OPMs

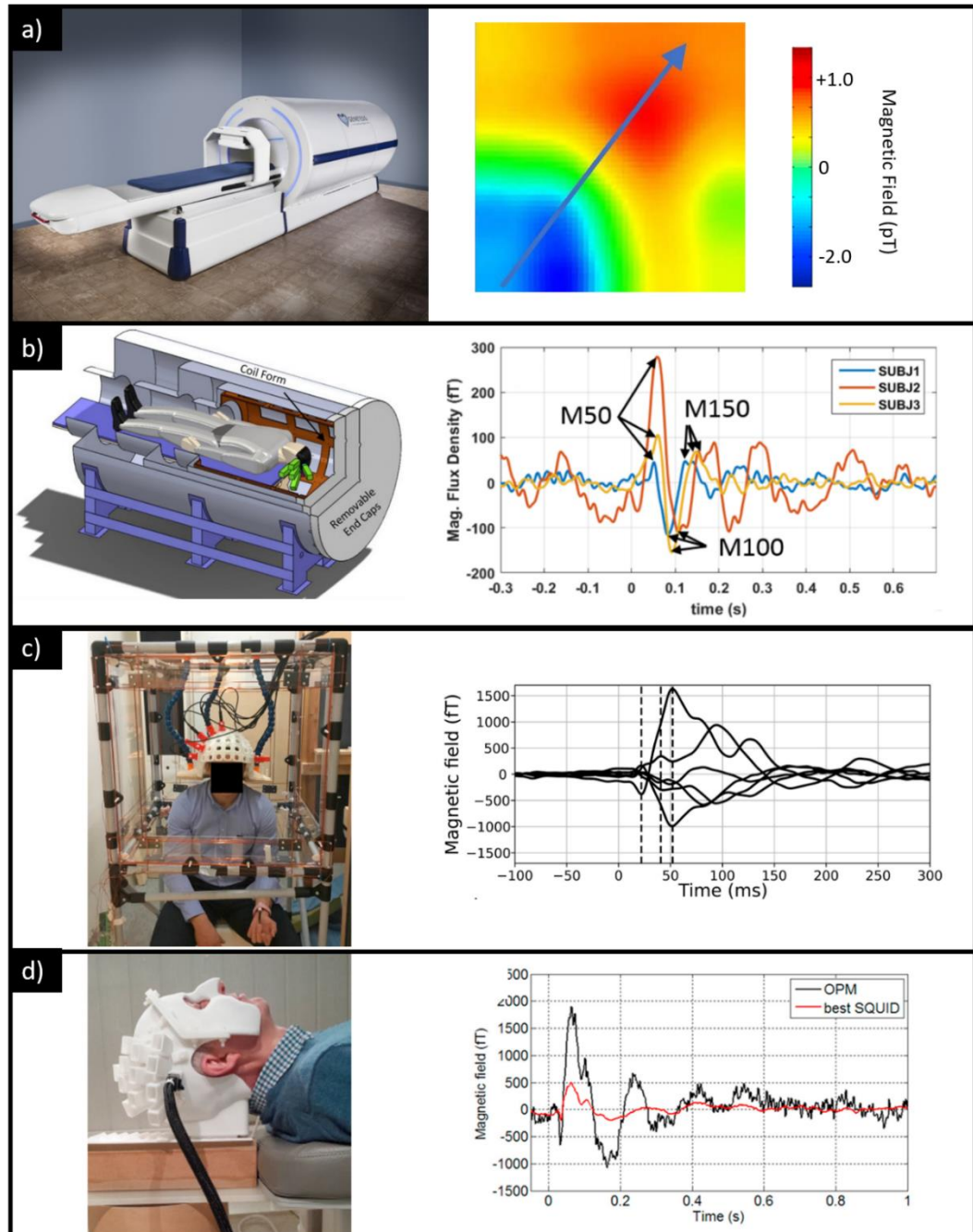


Figure 3.2: Methods of mounting OPMs. Four example methods of mounting OPMs in order to detect biomagnetic signals, with corresponding data from each setup. a) The Genetesis CardioFlux Magnetocardiograph™ holds sensors above the participant's chest inside the cylindrical shield (Pena et al., 2020). The data is a magnetic field map of heart beats averaged together over 90 seconds. b) A similar set-up to a) used by Borna et al. (Borna et al., 2017) but with OPMs mounted around the participant's head. The data shown is from an auditory evoked response. c) The set-up used by Iivanainen et al. (Iivanainen et al., 2019b) where a similar helmet design to a cryogenic system placed in the centre of the MSR holds the sensors and allows them to be pushed onto the participant's scalp. The data shows a median nerve evoked response. d) The 3D printed sensor cast solution used by Boto et al. (Boto et al., 2017) that holds the sensors directly on the participant's scalp using a helmet based on their MRI. This data also shows a median nerve evoked response.

3.2 The QuSpin OPM

At the time of writing, QuSpin have developed two generations of OPM sensor design, both of which are used in the experimental chapters of this thesis. The first generation sensor (Gen-1) first became available in early 2016. It consists of a $3 \times 3 \times 3 \text{ mm}^3$ glass cell filled with rubidium-87 (^{87}Rb) placed 6 mm from the external face of the sensor casing (Figure 3.3a). The casing has external dimensions of $13 \times 19 \times 110 \text{ mm}^3$, and the whole sensor head weighs 20 g. The second generation (Gen-2) became available in late 2018. It also contains a glass cell 6.5 mm from the tip of the sensor but is offset by 2 mm from the centre of the sensor (i.e. is asymmetric), and has a smaller external casing of $12.4 \times 16.6 \times 24.4 \text{ mm}^3$ (Figure 3.3b) with a total sensor head weight of 4 g. The basic operation of both generations is the same and the components inside the casing are connected to a control electronics box via a 6.5 m cable. However, the Gen-1 sensor uses a single stretch of cable that weighs 33 g/m, whereas the Gen-2 sensor first has a 60-cm flex cable from the sensor head before connecting to a Gen-1 style cable.

The glass cell is heated to 150°C using resistive coils to create a high density rubidium gas vapour. A 795-nm wavelength diode laser placed inside the sensor casing that provides the optical pumping. The light is circularly polarised, and reflected through the glass cell before reaching a photodetector which measures the intensity of the transmitted laser light (Figure 3.3c). The cell is surrounded by three orthogonal electromagnetic coils which help to control background field inside the cell. In the Gen-1 sensor, the coils are configured as two pairs of rectangular coils connected in series along the x- and y-axes, and a single rectangular coil at the tip of the sensor along the z-axis. The Gen-2 sensor has all three coils configured as pairs (see Figure 3.3d for both configurations). By applying currents to the coils, magnetic fields are generated in the x, y, and z directions in order to offset background magnetic fields up to 50 nT through an automated field-zeroing procedure (Shah and Hughes, 2015).

The coils also provide a modulation signal across the cell to obtain directional sensitivity (this will be described in detail later).

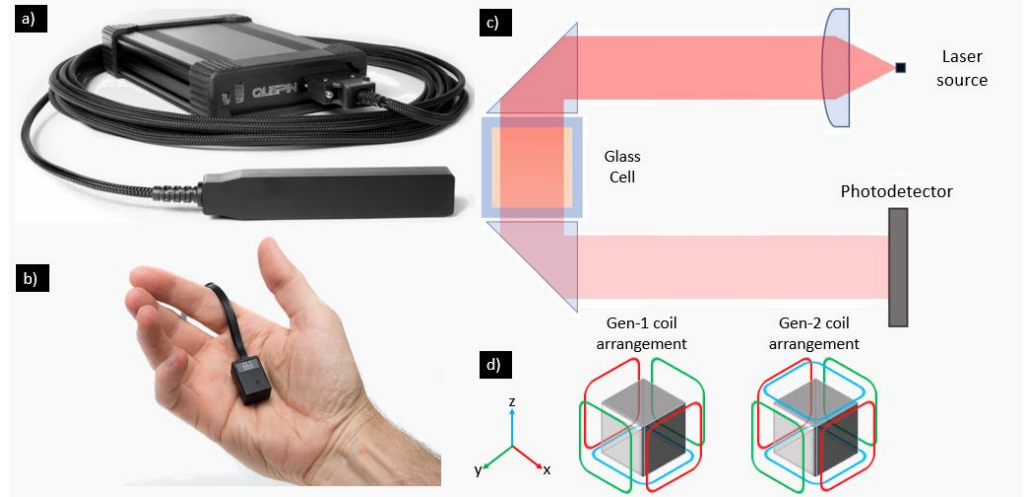


Figure 3.3: The QuSpin OPM. a) The Gen-1 OPM sensor connected to an electronics unit via a 6.5 m cable. b) Gen-2 OPM sensor which has a smaller sensor casing. This is also connected to an electronics unit but has an additional 0.6 m of flex cable. c) Laser propagation through the cell and onto the photodetector. d) Electromagnetic coil configuration around the glass cell for Gen-1 and Gen-2 sensors. Adapted from Osborne et al. (Osborne et al., 2018).

We will now move on to look in detail at the physical principles which enable OPMs to sensitively measure magnetic fields.

3.3 Optical pumping

Optical pumping is a method of transferring angular momentum from a light source to a sample of atoms so that nearly all atoms in the sample occupy the same quantum state. Alkali metals, such as ^{87}Rb , are particularly useful to use in optical pumping as they have only one electron in their outermost shell that can be manipulated, allowing precise control of a spin ensemble. The total atomic angular momentum of a particle $\mathbf{F}$ is given as

$$\mathbf{F} = \mathbf{J} + \mathbf{I} \quad [3.1]$$

where $\mathbf{J}$ is the angular momentum of the electron and $\mathbf{I}$ is the angular momentum of the nucleus. For ^{87}Rb , the nuclear spin is $I = 3/2$, but the electron angular momentum consists of its orbital angular momentum $\mathbf{L}$ and its spin $\mathbf{S}$ i.e.

$$\mathbf{J} = \mathbf{L} + \mathbf{S} . \quad [3.2]$$

3.3.1 Fine structure

The spin of an electron is described by the spin quantum number $S = 1/2$. If the single valence electron of an alkali metal is in its ground state, its orbital angular momentum is described by the quantum number $L = 0$, and the excited state by $L = 1$. These two states are further affected by interactions within the atom. The first interaction we consider is that between the electron and the nucleus. Classically, we think of an electron as orbiting the nucleus. Therefore, if we shift the frame of reference to the electron, we can equally think of the positively charged nucleus rotating around the electron. The relative motion of the nucleus acts like a current loop, generating a magnetic field. The electron also has a magnetic field due to its charge and spin, and the interaction between these two fields leads to ‘fine structure’ splitting in the atomic energy levels, defined by the quantum number J which can take values in the range $|L - S| \leq J \leq |L + S|$ in integer steps. By using this criteria, for the $L = 0$ state (the ground state), only one fine structure level exists at $J = 1/2$. However, the $L = 1$ state (the excited state) has two possible fine structure states at $J = 1/2$ and $J = 3/2$. This means that two possible transitions from the ground state ($L = 0, J = 1/2$) exist: the D1 transition to the first excited state ($L = 1, J = 1/2$), and the D2 transition to the second ($L = 1, J = 3/2$) (see Figure 3.4).

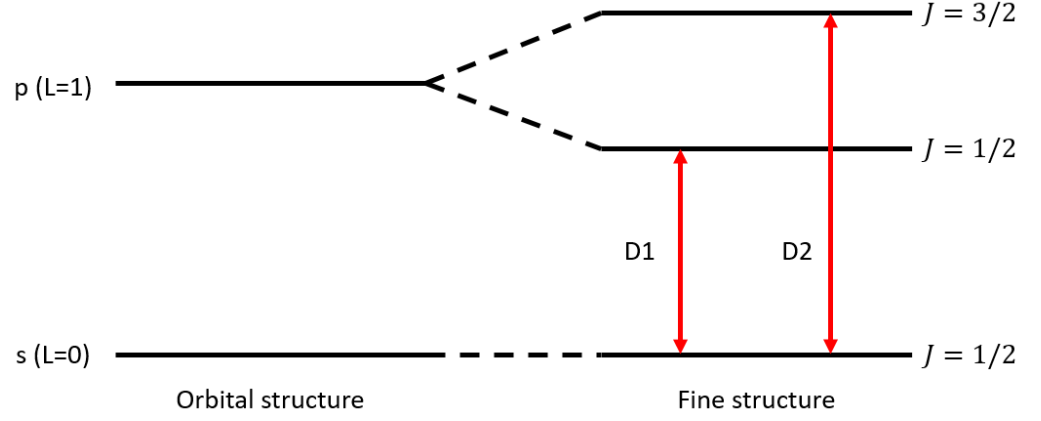


Figure 3.4: Fine structure splitting. Splitting of the energy levels due to the fine structure of the ground (*s*) and excited (*p*) states. Two transitions are possible (*D1* and *D2*) due to the absorption of resonant photons.

These transitions can occur through the absorption of a photon with energy equal to the energy difference between the two states. The energy of a photon is given by

$$E = h\nu = \frac{hc}{\lambda}, \quad [3.3]$$

where h is Planck's constant, c is the speed of light in a vacuum, ν is the frequency of the incident light, and λ is the wavelength of the incident light. The QuSpin sensor exploits the D1 transition of ^{87}Rb which requires photon energy of 1.56 eV, achieved using a light source with wavelength 795 nm.

3.3.2 Hyperfine structure

A second splitting of the fine structure levels creates a hyperfine structure, and occurs due to interactions between the nuclear spin I and the magnetic field due to the electron spin S . If we focus on the D1 transition, where $J = 1/2$ and $I = 3/2$ for both the ground and excited states, the total atomic angular momentum is given by $F = I \pm J$, and so two hyperfine levels exist for each state: $F = 1$ and $F = 2$ (Figure 3.5). The hyperfine splitting is a small effect compared to the fine structure, such that the bandwidth of a laser does not allow it to selectively target transitions between the hyperfine states.

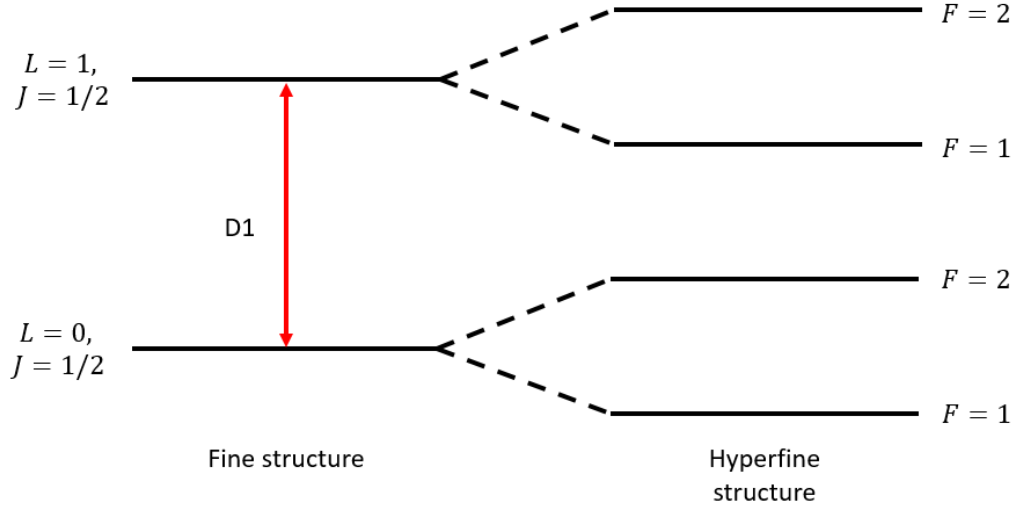


Figure 3.5: Hyperfine splitting. Further splitting of energy levels due to interactions between nuclear and electron spin for the D1 transition of ^{87}Rb .

3.3.3 Zeeman structure

A third and final splitting occurs due to any interaction of the atom with a magnetic field. This is called Zeeman splitting and occurs along a quantisation axis. With zero applied magnetic field, the quantisation axis is along the direction of the laser propagation as it passes through the cell, and the different states are degenerate (i.e. they have the same energy level). However, in the presence of a magnetic field, the orientation of the atomic angular momentum relative to the field becomes important, resulting in different atomic energy levels. The projection of the Zeeman splitting sublevels is described by $m_F = [-F, -F + 1, \dots, F - 1, F]$. Therefore, for the $F = 1$ hyperfine state, $m_F = [-1, 0, 1]$, and for $F = 2$, $m_F = [-2, -1, 0, 1, 2]$ (Figure 3.6).

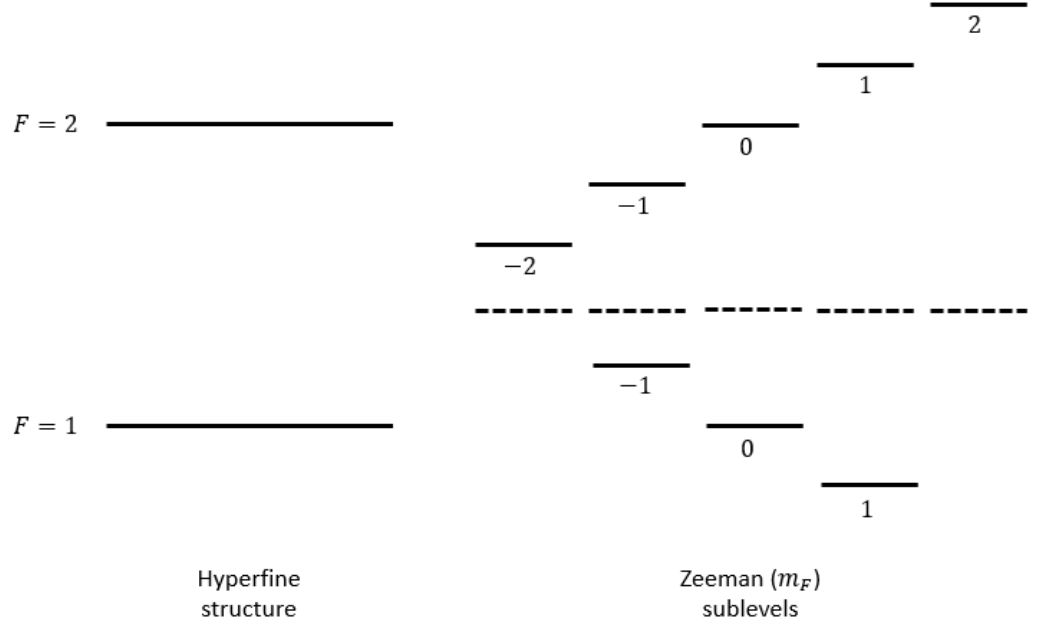


Figure 3.6: Zeeman splitting. A final splitting of the energy states due to the interaction with a magnetic field. Dashed lines show degeneracy when no magnetic field is present.

The energy difference between each Zeeman state is given by

$$\Delta E = g_F \mu_B B, \quad [3.4]$$

where g_F is the hyperfine Lande g-factor, μ_B is the Bohr magneton, and B is the magnetic field. The magnetic moment of an electron in this magnetic field precesses at the Larmor frequency

$$\omega = \gamma B, \quad [3.5]$$

where γ is the gyromagnetic ratio. For the unpaired electron in ^{87}Rb , the gyromagnetic ratio is given as

$$\frac{\gamma_F}{2\pi} = \frac{g_F \mu_B}{\hbar}. \quad [3.6]$$

The Lande g-factor for ^{87}Rb in the $F = 1$ state is $g_F = -1/2$, and for $F = 2$, $g_F = +1/2$. The change in sign means that the electron spin precesses in opposite directions depending on which state it is in.

The 795-nm laser in the QuSpin sensor induces a D1 transition in the ^{87}Rb in the glass cell. The laser light is σ^+ circularly polarised meaning each photon has angular momentum of +1 along the beam direction. This additional angular momentum is transferred to the atom providing it obeys the selection rule $\Delta m_F = m_{F_{final}} - m_{F_{initial}} = +1$. Following absorption of a photon, the atom (now in its excited state) returns to the ground state by emitting a randomly polarised resonant photon, which can depolarise another atom if absorbed. The atom can then be repolarised providing the selection rule can still be applied. The combination of the D1 transition pumping and the spontaneous emission of photons drives the atom into the ground state with the highest angular momentum (i.e. $L = 0$, $F = 2$, $m_F = 2$). This state is known as the 'dark state' as the atom becomes insensitive to the incident laser light as there are no available levels with $m_F > 2$. As the process repeats for all atoms, the ^{87}Rb vapour becomes transparent to the laser light. In this state, the intensity of light detected at the photodiode is at its maximum. Figure 3.7 shows a summary of the optical pumping transitions.

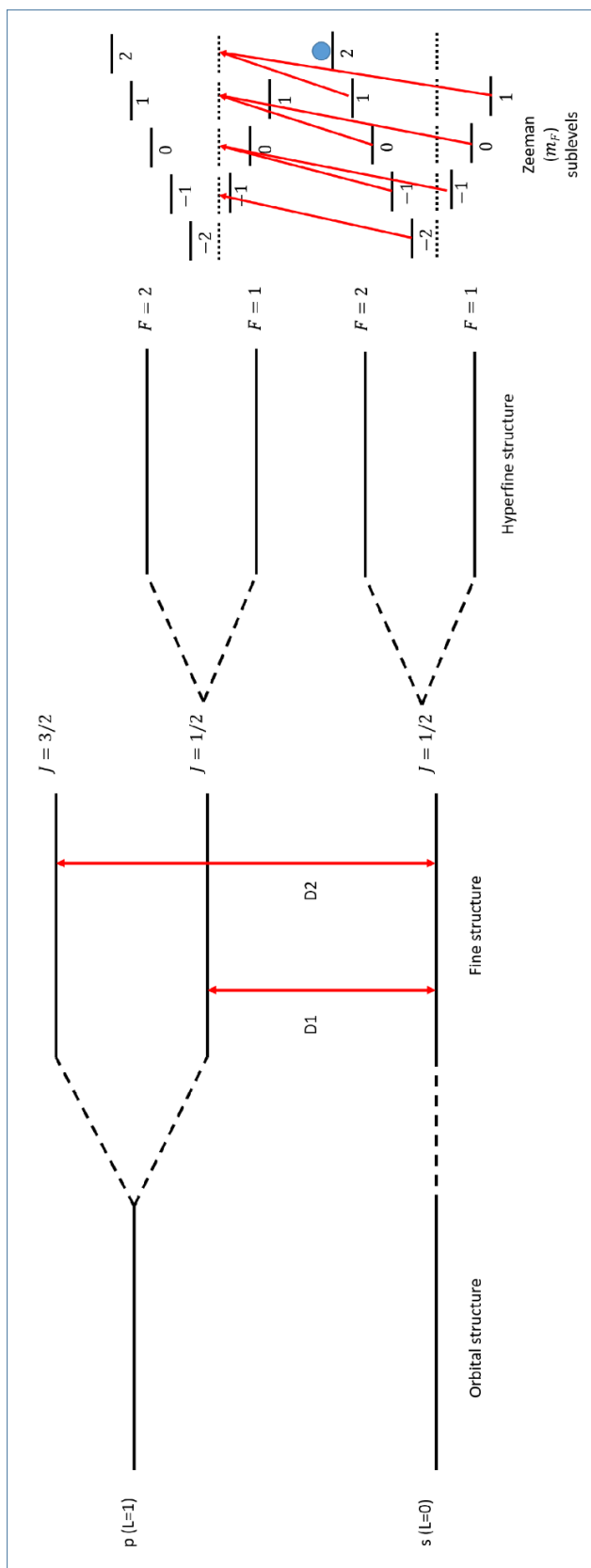


Figure 3.7: Optical pumping transitions. Summary of the energy level transitions induced by optical pumping on the D1 transition line using σ^+ circularly polarised light.

3.4 Spin-Exchange Relaxation Free (SERF) regime

As more and more atoms transition into the transparent dark state and the cell becomes transparent to laser light, a strong net magnetisation is produced along the laser axis as the ensemble of spins precess coherently. This is called **spin polarisation**, and the resulting system is magnetically sensitive. However, the coherence of the spins can be destroyed through several processes such as spin-exchange collisions between atoms, collisions with the walls of the cell, and interactions with the laser. The dominant mechanism is considered to be the spin-exchange collisions.

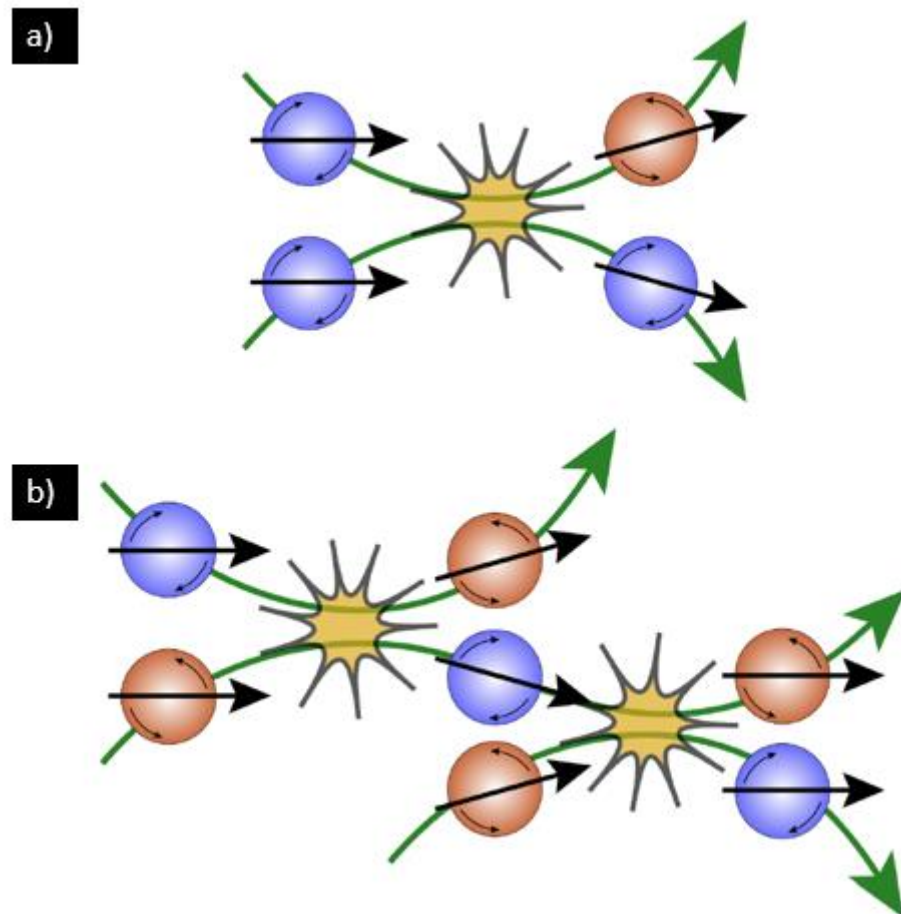


Figure 3.8: Spin-exchange collisions. a) Spin-exchange collision between two atoms in the same state. The total angular momentum is conserved but the atoms may switch hyperfine levels causing them to precess in the opposite direction causing decoherence. b) In a high density, low magnetic field environment, the time between collisions is much shorter than the precessional frequency and so atoms rapidly switch between hyperfine states. Figure adapted from Seltzer (Seltzer, 2008).

When two ^{87}Rb atoms collide, the total angular momentum is conserved, but the hyperfine levels of the atom may change. For example, in Figure 3.8a, two atoms are facing the same direction and are both in the same F-state so they precess in the same direction too. After collision, both atoms still point in the same direction, but one of the atoms changes its F-state meaning it now precesses in the opposite direction. This difference in precession rapidly decoheres the system. The relaxation rate due to spin-exchange collisions is given as

$$R_{SE} = \frac{1}{T_{SE}}, \quad [3.7]$$

where T_{SE} is the time between spin-exchange collisions. However, in a sufficiently low magnetic field environment and with high atomic density, the spin exchange rate increases to $R_{SE} \gg \gamma B$. This environment shuts down the spin-exchange relaxation as the atoms rapidly switch between the $F = 1$ and $F = 2$ states (see Figure 3.8b). The atoms precess an infinitesimal amount between each collision, but as there are more m_F sublevels in the $F = 2$ there is a net positive precession in the system. In this regime, the atoms precess coherently but at a lower rate described as

$$\omega_0 = \frac{\gamma B}{Q(P)}. \quad [3.8]$$

$Q(P)$ is the nuclear slowing down factor which is a function of the total polarisation of the system P . For a fully polarised system (i.e. the $F = 2$, $m_F = 2$ hyperfine state), spin-exchange collisions have no effect as there are no other m_F levels that can accommodate the angular momentum. As the polarisation decreases, the spin distribution across the m_F levels increases, which in turn increases the slowing down factor $Q(P)$ due to atoms rapidly switching hyperfine levels. The slowing down factor is expressed as

$$Q(P) = \frac{6+2P^2}{1+P^2}. \quad [3.9]$$

This regime is the basis of the spin-exchange relaxation free (SERF) magnetometer. By suppressing the spin exchange relaxation, the coherence time of the magnetometer is dramatically longer, and the increase in atomic density also allows for an increased signal.

3.5 Signal equations

Following the optical pumping and spin-exchange suppression, there is a polarisation $\mathbf{P}$ in the glass cell along the direction of the laser (which we will treat as the z direction). This polarisation is sensitive to magnetic fields and can be described using the Bloch equations (Bloch, 1946, 1953):

$$\frac{d\mathbf{P}}{dt} = \frac{1}{Q(P)} \left[\gamma \mathbf{P} \times \mathbf{B} - (\mathbf{P} - P_0 \hat{z}) \frac{1}{T} \right], \quad [3.10]$$

where $Q(P)$ is again the nuclear slowing down factor, γ is the gyromagnetic ratio of the electron, P_0 is the equilibrium polarisation obtained by optical pumping when the cell experiences zero magnetic field, and $T = (R + 1/T_2)^{-1}$ where R is the optical pumping rate and T_2 is the relaxation time of the system.

As we are considering the laser to be in the z direction, the light passing through the cell is only sensitive to the P_z component of the polarisation. In steady state (i.e. $\frac{d\mathbf{P}}{dt} = 0$), the solution to equation 3.10 is

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

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

$$P_z = \frac{\left(\frac{1}{\gamma T}\right)^2 + B_z^2}{\left(\frac{1}{\gamma T}\right)^2 + B_x^2 + B_y^2 + B_z^2} P'_0, \quad [3.11]$$

where $P'_0 = P_0 RT$. If we set the magnetometer to measure fields perpendicular to the laser (in this case B_x), B_y and B_z are set to 0, simplifying the equations in 3.11 to

$$\begin{aligned} P_x &= 0 \\ P_y &= \frac{-\gamma T B_x}{1 + (\gamma T B_x)^2} P'_0 \\ P_z &= \frac{1}{1 + (\gamma T B_x)^2} P'_0. \end{aligned} \quad [3.12]$$

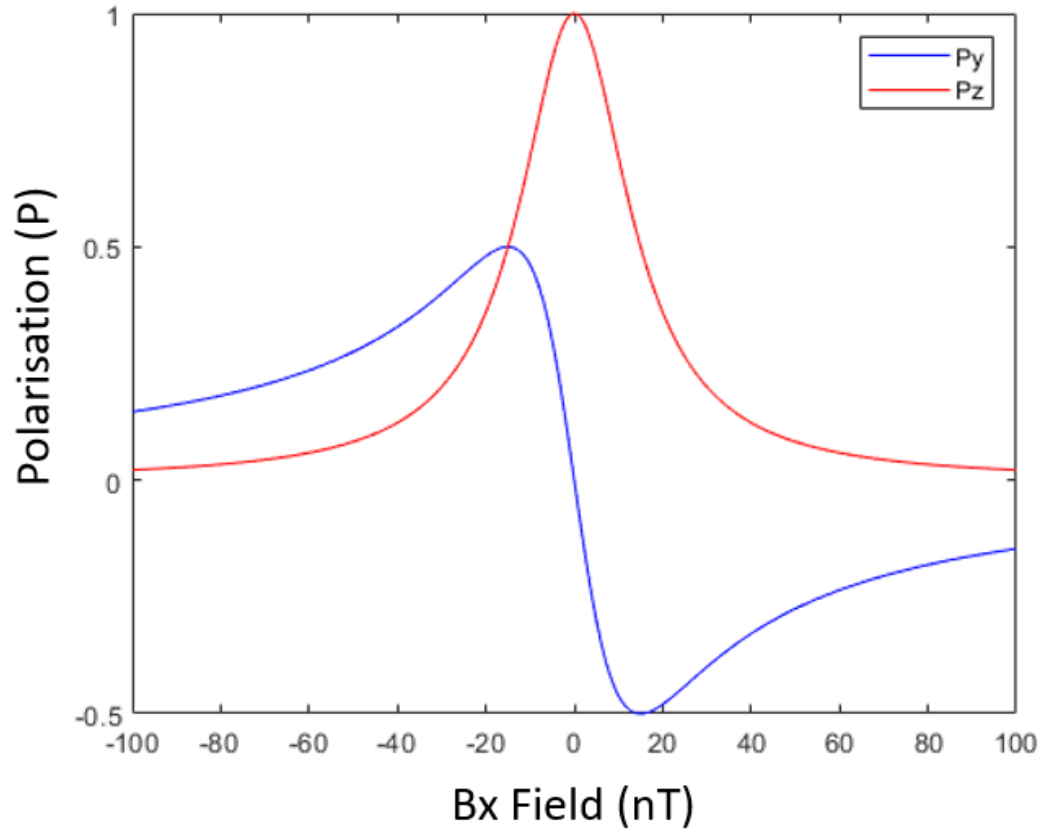


Figure 3.9: Bloch equation solutions. The polarisation in the y-direction takes the form of a dispersion curve, while in the z-direction it follows a Lorentzian zero-field resonance curve. The z polarisation has a full width half maximum of $\frac{2}{\gamma T} = 30$ nT.

Figure 3.9 shows these curves plotted as a function of B_x . The z component of the polarisation takes a Lorentzian line shape (also known as the

zero-field or Hanle resonance (Hanle, 1925). The full width at half maximum is $2/\gamma T$ which is roughly 30 nT for QuSpin sensors. There are however, two issues with this setup: 1) it is sensitive to low frequency $1/f$ noise, and 2) the symmetry of the Lorentzian line means that equal positive and negative changes in the magnetic field have the same output. In order to solve issue 2, we apply an oscillating magnetic field in the measurement direction (in this case, B_x). The applied magnetic field modulates the amplitude of the polarisation at a frequency much larger than the relaxation rate of the atomic vapour: for the QuSpin sensor, the relaxation rate is of the order 100 Hz (this also determines the bandwidth of the OPM), and the sensor uses a modulation frequency of 923 Hz. The field is produced by applying an oscillating current to the coils surrounding the cell (described in section 3.2). The expression for the rate of change of polarisation must now be updated to include the modulation term:

$$\frac{d\mathbf{P}}{dt} = \frac{1}{Q(P)} \left[\gamma \mathbf{P} \times [\mathbf{B} + b_x \cos(\omega t) \hat{x}] - (\mathbf{P} - P_0 \hat{z}) \frac{1}{T} \right], \quad [3.13]$$

where $b_x \cos(\omega t)$ is the modulation term with field amplitude b_x , and angular frequency ω . This also means that the solutions in equations 3.11 and 3.12 must be updated. If we evaluate for P_z and again assume $B_y = B_z = 0$, we reach

$$P_z = \frac{\gamma T B_x}{1 + (\gamma T B_x)^2} J_0 \left(\frac{\gamma b_x}{Q(P) \omega} \right) J_1 \left(\frac{\gamma b_x}{Q(P) \omega} \right) P'_0 \sin(\omega t), \quad [3.14]$$

where J_n are Bessel functions of the first kind. These functions complicate the signal equation but they can be evaluated to a constant term. This allows us to write equation 3.14 as

$$P_z \propto \frac{\gamma T B_x}{1 + (\gamma T B_x)^2} P'_0. \quad [3.15]$$

We can then use a lock-in amplifier to extract the amplitude of a known oscillating signal whilst strongly rejecting background noise at other frequencies. It achieves this by multiplying the input signal with a reference signal then applying an adjustable low-pass-filter to the result. After lock-in detection of the photodiode voltage V at the modulation frequency, we get the final signal output from the OPM:

$$V \propto \frac{\gamma T B_x}{1 + (\gamma T B_x)^2}. \quad [3.16]$$

If we now evaluate V as a function of B_x , the result is a dispersion curve that allows us to distinguish between positive and negative field changes (see Figure 3.10). For sufficiently low field changes (i.e. where $\gamma T B_x \ll 1$), we can take the Taylor expansion of $V(B_x)$ to get a linear equation:

$$V \propto \gamma T B_x. \quad [3.17]$$

The change in magnetic field is a simple field per unit voltage calculation. As this is an approximation, the larger the field changes that occur, the less accurate the linear estimation is. For QuSpin sensors, this linear region is in the range of approximately ± 5 nT. Changes over this range induce gain changes of up to 10% (Osborne et al., 2018), while changes of ± 1.5 nT reduce this error to 5% (Boto et al., 2018).

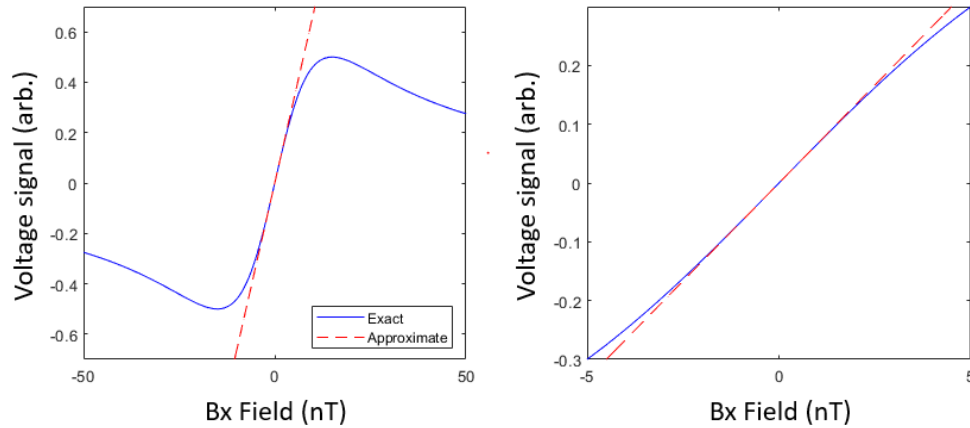


Figure 3.10: Voltage output of an OPM. By applying a modulation field, the voltage output shows a dispersion curve that allows positive and negative field changes to be distinguished. For small changes in magnetic field, the curve is approximately linear.

3.6 QuSpin OPM array

Both Gen-1 and Gen-2 OPM sensors are attached to an electronics unit which provides both control and readout of the sensor. The sensor is controlled using QuSpin software that interfaces with the electronics unit through a USB connection. On initialisation the software performs three tasks. First, it applies a current to the resistive coils around the cell to increase the temperature of the cell to achieve the necessary spin density. Second, the laser is simultaneously powered on and stabilised to the correct frequency for optical pumping of the D1 transition for ^{87}Rb . Finally, the modulation signal is generated in the coils surrounding the cell.

As we need a multi-channel system to perform MEG, OPMs must be operated simultaneously in an array to record information from multiple positions around the head. There are several considerations when operating multiple OPM channels simultaneously. The first is the modulation signal. This signal has to be common for all sensors as small differences in the amplitude or phase of the signal generated by each sensor can affect the recordings. In order to do this, the modulation signal is generated by a single electronics unit (the 'master' unit) and is passed through to the other 'slave' units. Likewise, the heater frequency of each OPM must also share a common source otherwise

the slight error in in each OPM results in low frequency noise (<10 Hz) (this is discussed in greater detail at the end of Chapter 6).

All channels must also have the same voltage-to-field calibration value. The coils around the cell are energised to create a known field within the cell, and the output of the sensor is measured and calibrated to ensure a set voltage per nanotesla response. The QuSpin sensors have three analogue output gain settings over a ± 4 V range: 1) the standard setting has a calibration value of 2.7 V/nT that provides a dynamic range of ± 1.5 nT; 2) the 3x gain setting has a value of 8.1 V/nT with a range of ± 0.5 nT; 3) the 0.33x gain setting has a value of 0.9 V/nT with a range ± 4.5 nT. For all measurements in this thesis, we use the standard 2.7 V/nT setting.

The operation of all channels simultaneously in close proximity can also cause an interference problem known as ‘cross-talk’. Cross-talk arises due to the fields generated by the modulation coils in one sensor in the array being detected by the surrounding sensors. The interference has an effect on both the sensor gain and the sensitive orientation of the sensor, such that a radial measurement of the magnetic field can be offset (Boto et al., 2018; Tierney et al., 2019a). However, it is possible to both model these interference fields to remove the effects from the data (Roberts, 2020), and improve the coil designs so that the interference effects can be reduced (Nardelli et al., 2019).

The data from each sensor can be recorded through either a digital or analogue output. The digital output is through the USB connection and can sample at a rate of 200 Hz. However, the analogue output can be recorded at much higher frequencies using an analogue-to-digital converter (ADC). In all experiments in this thesis, data were recorded using the analogue output sampling at 1,200 Hz.

The magnetic shielding offered by a typical MSR (resulting in remanent fields of the order of tens of nanotesla) can just about allow the QuSpin OPMs to perform their field zeroing procedure (they can null fields up to 50 nT). However, the system must remain static as a rotation of 3 degrees in a 30 nT field is enough to generate a 1.5 nT change in field, which would cause a significant (5%) change in gain. In addition, any drift in the remnant magnetic field greater than 1.5 nT will cause the same issues. In order to ameliorate these problems, bi-planar nulling coils can reduce the strongest remnant field component by a factor of 53, and the strongest gradient by a factor of 7 (Holmes et al., 2018; Holmes et al., 2019). This allows the OPMs to stay within their dynamic range during experiments, as well as allowing the participant to perform naturalistic movements (Boto et al., 2018; Roberts et al., 2019).

Figure 3.11 shows the system overview prior to the work presented in this thesis, as described in Boto et al. (Boto et al., 2018). 13 Gen-1 QuSpin OPMs were mounted on the head, and a further 4 Gen-1 OPMs were used as a reference array (Figure 3.11b). The sensors are mounted on the head using a scanner-cast (3.11c) which was based on the participant's MRI to provide accurate knowledge of sensor location and orientation relative to the brain.

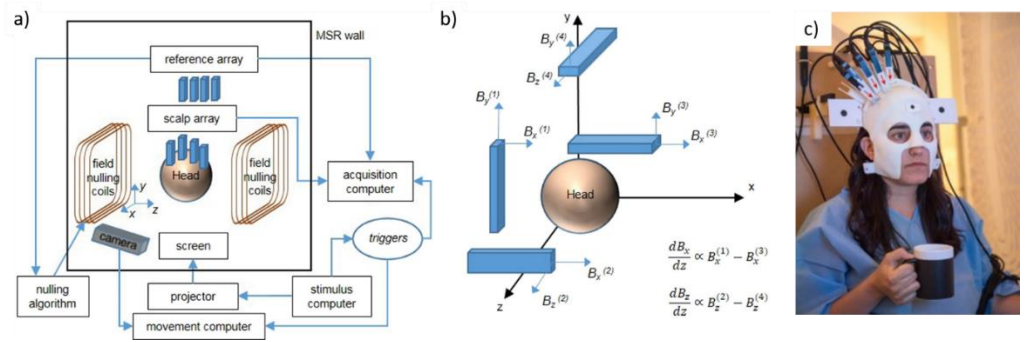


Figure 3.11: System overview prior to the work in this thesis. a) An overview of the system used in Boto et al. (Boto et al., 2018). b) The reference sensor array placed behind the participant. c) The scanner-cast method of mounting the sensors on the participant's head with accurate knowledge of the sensor locations and orientations.

Chapter 4: Designing a generic OPM-MEG helmet

This chapter details the simulations, design, construction, and pilot experiments for a prototype OPM-MEG system. Specifically, this system employs a generic helmet, which will have utility across the lifespan from babies to adults. We begin with simulations to validate the helmet theoretically. We also describe a method for managing the temperature of the OPM sensors to ensure that the sensors do not overheat and to keep the participants safe. Following this, a co-registration technique is devised, and a finger abduction experiment performed on three participants to validate the use of our generic helmet to detect, record and localise MEG signals. The design and methods successfully enabled recording of high fidelity MEG data from three participants performing a finger abduction task, as well as allowing localisation to the expected regions of the brain in all three participants, according to the Oxford-Harvard probabilistic atlas. The results presented here have been published in Hill et al., Nature Communications (Hill et al., 2019).

4.1 Introduction

The fundamental building blocks of human cognition are laid down within the first decades of life. In the early years, capabilities such as movement, language and social interaction develop; during later years (late childhood and adolescence), cognitive and attentional mechanisms further evolve alongside finer motor skills. However, relatively little is known about maturation of brain function during these critical times. Brain imaging provides a wealth of information on both the structure and function of the brain, but limitations in technologies such as magnetic resonance imaging (MRI) or magnetoencephalography (MEG) are exposed when attempting to investigate neurodevelopment, in particular during naturalistic tasks. This is for two reasons: firstly, scanner technology tends to be optimised for adults, and the difference in the head-sizes of infants and adults is problematic for some systems. Younger participants are also less able to tolerate the imaging environment and excessive movement negatively impacts data quality. In clinical practice, participants are often sedated to prevent excessive movement, however this approach is not feasible when studying brain function. These limitations prohibit us from asking key neurodevelopmental questions in younger participants. Secondly, the unnatural environments presented by most neuroimaging modalities impose significant limitations on the type of experimental paradigm that participants can undergo. For example, restricted head movements make it hard to interact naturally with engaging tasks. Similarly, restricted movement, coupled with limited space inside the scanner, make it hard to allow participants to undertake natural learning experiences. To date, the best functional imaging solutions, both for measurement in infants and for naturalistic experimentation, involve wearable technologies, such as electroencephalography (EEG). However, EEG is limited, as it is highly susceptible to artefacts from electrical activity in muscles (Boto et al., 2018; Boto et al., 2019; Claus et al., 2012; Muthukumaraswamy, 2013) and lacks spatial precision (Baillet, 2017). If we are to understand the

developmental trajectory of human brain function, and its perturbation by disorders, then new technologies are required.

Here, we aim to solve this problem by creating a wearable MEG system with complete lifespan-compliance. OPMs (like the ones described in Chapter 3) are small and lightweight, and can ostensibly be positioned flexibly on the scalp surface. This means that an OPM-MEG system can, in principle, be adapted to any head shape/size. Furthermore, if background magnetic fields are appropriately nulled (Holmes et al., 2018), OPMs can be mounted on the head and participants can move during scanning. Initial work by Boto et al. (Boto et al., 2018) showed proof of principle of OPM-MEG, with high fidelity data captured whilst a participant moved freely. This initial study highlighted the excellent promise of OPM-MEG for lifetime compliant scanning.

There are a number of significant challenges that must be addressed before a practical OPM-MEG system could be deployed in children:

- 1) The initial prototype system in Boto et al. (Boto et al., 2018) used heavy and costly 3D printed helmets for sensor mounting. Those helmets, which were customised for each individual participant, are not appropriate for use in infants and young children. Further, the inability to adapt the helmets to different head shapes/sizes meant the high cost precluded their use in large cohort studies. We must therefore design a generic and ergonomic helmet that can address these issues.
- 2) If we use generic helmet then, unlike the case for the bespoke helmets, we don't know the locations and orientations of the sensors. This information is vital for source reconstruction, where errors of only a few millimetres can have a significant detrimental effect, and so a co-registration technique is needed.
- 3) OPM cells are heated to $\sim 150^{\circ}\text{C}$ to keep the alkali vapour in the SERF regime (as described in Chapter 3). Although the outer casing of the OPM typically remains at body temperature, this relies on efficient

removal of heat (e.g. being in contact with open air). When placed inside a helmet, a large surface area of the OPM becomes insulated, removing its exposure to open air which causes the outer casing to heat up. This temperature needs to be controlled to ensure a safe scanning environment for the participants, as well as to prevent the sensors overheating and getting damaged.

In this chapter, we aim to develop a practical system for use across the lifespan. Using simulations, we assess theoretically the signal strengths expected from a generic system (Boto et al., 2016). These simulations address specifically the challenges of scanning a paediatric population. Based on these simulations, we then describe a redesign of the original system to incorporate a simple and ergonomic helmet which is practical in children and offers genuine lifespan compliance. We also assess the temperature management of the sensors while inside the helmet to ensure neither the sensors nor the participants overheat.

4.2 Simulations

Successful fabrication of an OPM-MEG system requires the design of an optimised helmet, balancing practicality and ergonomics with sensitivity. To understand how helmet design impacts the measurable MEG signal, we undertook a set of simulations (similar to Boto et al. (Boto et al., 2016)).

4.2.1 Methods

A hypothetical 81-channel OPM array was simulated with sensor locations following, approximately, a 10-10 EEG arrangement¹. For

¹ This is the 10-10 international standard system for electrode placement in EEG, where the spacing between electrodes is 10% of the total front–back and right–left distance of the skull.

comparison, we also simulated a cryogenic array. The designs were as follows (also shown in Figure 4.1):

- 1) A bespoke helmet, where OPMs are placed directly on the scalp surface, similar to 3D printed helmets used in previous work (Boto et al., 2018; Boto et al., 2017). The scalp surface was extracted from an anatomical MRI of a 2-year-old, selected at random from the Pediatric Brain Atlas (Brain-development.org, 2018). Sensor locations were placed directly on this individual's head surface.
- 2) A generic helmet based on the average head shape of a 2-year-old child. The average head shape was found by accessing 33 MRI anatomical images from the Pediatric Brain Atlas. The scalp surface was extracted from each anatomical, and a k-dimensional tree (Bentley, 1980) searched for the nearest neighbours between two of the scalp meshes. The midpoint between each pair of vertices was found, creating a new average surface. This process was repeated for each of the 33 anatomical images in turn, and the average surface updated. The vertices of the average surface were extended along their normals by the standard deviation of the individual surfaces, to generate a surface that would accommodate 95% of 2-year-old head shapes, and this became the inner surface of the simulated helmet. Having derived this inner surface, it was fitted, visually, to the MRI of the same 2-year-old used in (1).
- 3) Sensors placed on the inner surface of a bicycle helmet, designed to fit children aged 1 to 6 years. The inner surface of a bike helmet was digitised using a Polhemus system and fitted, visually, to the scalp of the same 2-year-old used in (1) and (2). Simulated sensors were placed on the inner helmet surface.
- 4) Finally, for comparison, the same 2-year-old's head was simulated inside a 275-channel adult CTF SQUID system; we simulated the head at the centre of the array, as well as resting against each of the sides and the top.

In all cases, the sensor orientations were assumed to be normal to the surface on which they were mounted.

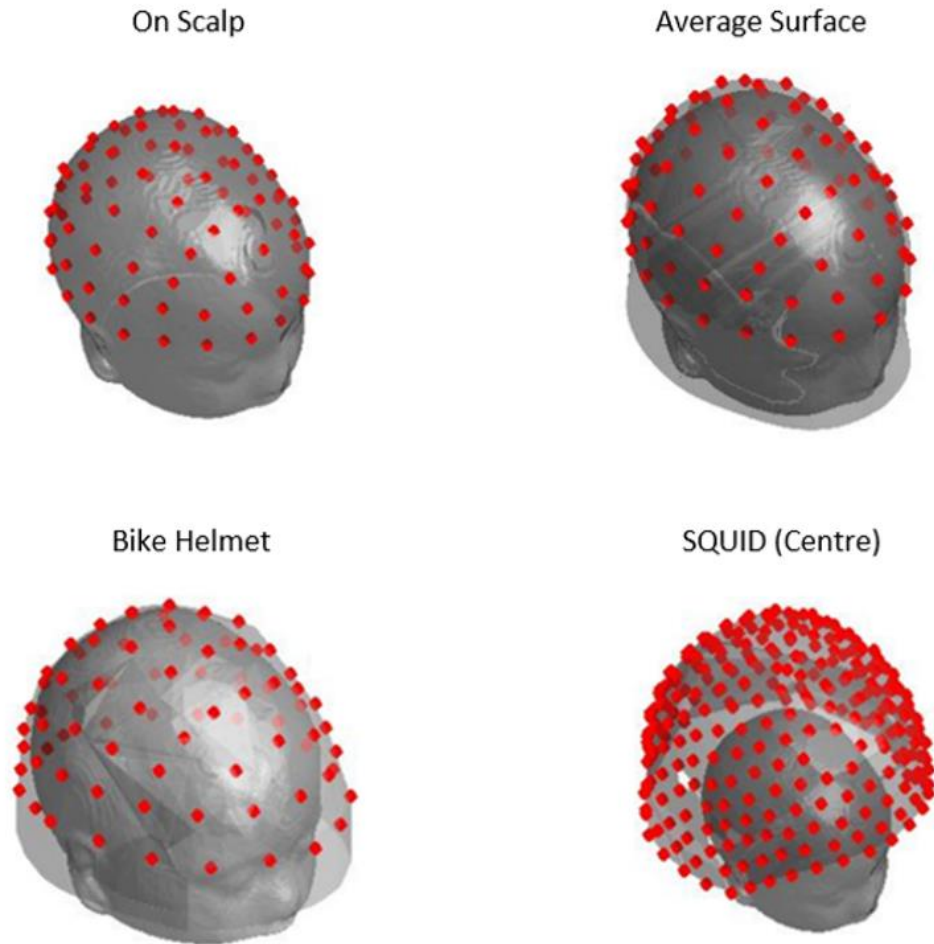


Figure 4.1: Simulated arrays. Layout of sensors on a 2-year-old's scalp in each of the 4 simulations.

Each of these geometries was the basis for a simulation in which we compared the different MEG helmet designs to obtain the magnitude of the measurable signal as a function of brain location. In terms of signal magnitude, clearly the bespoke helmet represents the ideal scenario in which the sensors are as close to the brain as possible. However, practical implementation of such a system would be difficult because 3D-printed helmets are intimidating, heavy, and expensive, with a new helmet having to be made for each individual. In terms of practicality, the bicycle helmet is desirable; it is easily sourced, cheap, and many participants can wear the same helmet. Moreover, it's

something that children will be familiar with; e.g. they could even take one home and practice with it at negligible cost.

For the simulation, the cortical surface was extracted from the anatomical MRI of a single 2-year-old, using Freesurfer (<http://surfer.nmr.mgh.harvard.edu/>). We simulated the fields from an array of dipoles (26,988 in total) that were distributed over the cortical surface with locally normal orientations. For each dipole we estimated the magnetic fields that would be measured at each sensor, for each of the 4 simulated geometries described above. The magnetic fields were derived using a spherical head model and the dipole solution first described by Sarvas (Sarvas, 1987). We assumed that the stand-off distance from the end of the sensor to the sensitive cell was 6 mm. For each dipole location, j , the dipole moment was assumed to be 1 nAm, and the simulated forward field vector, l_j , calculated. The Frobenius norm, f_j , of the forward field was then calculated as:

$$f_j = \|l_j\|_F = \sqrt{\sum_{i=1}^{N_{ch}} |l_{ij}|^2}, \quad [4.1]$$

where N_{ch} is the number of channels (81 for the OPM arrays and 275 for the SQUID array) and i indexes channel number. This resulted in 26,988 values of f_j for each of the 4 geometries, representing sensitivity of that specific geometry to all regions of the cortical surface. Following this, for each location, we divided the Frobenius norm of the forward field by the mean Frobenius norm, over all superficial dipole locations (i.e. those generating the largest signal), for the on scalp array helmet; this resulted in, approximately, a 0 to 1 scale for the measurable signal amplitude with values of 1 being closest to the on scalp helmet. This allowed us to quantitatively measure the sensitivity lost when using more practical helmet designs compared to the “gold standard”.

4.2.2 Simulation results

Figure 4.2 shows the simulated MEG signal strength in a 2-year-old child, using the four helmet designs described above: (A) a 3D printed bespoke helmet; (B), a generic helmet designed to fit 95% of 2-year-olds; (C) a standard child bike helmet; and (D) a cryogenic MEG system. Figure 4.2E shows the distribution of measurable signal values across all dipole locations for each helmet type. Although the bike helmet results in a drop in signal strength compared to the bespoke design as expected, it is simple, cheap, practical, suited to children, and it vastly outperforms cryogenic systems. This likely makes this shape a good compromise. For this reason, we chose to base our prototype helmet on a bike helmet. This would allow a simple means to mount sensors, and an easy way to expand the system to fit a range of head sizes just by changing the helmet size.

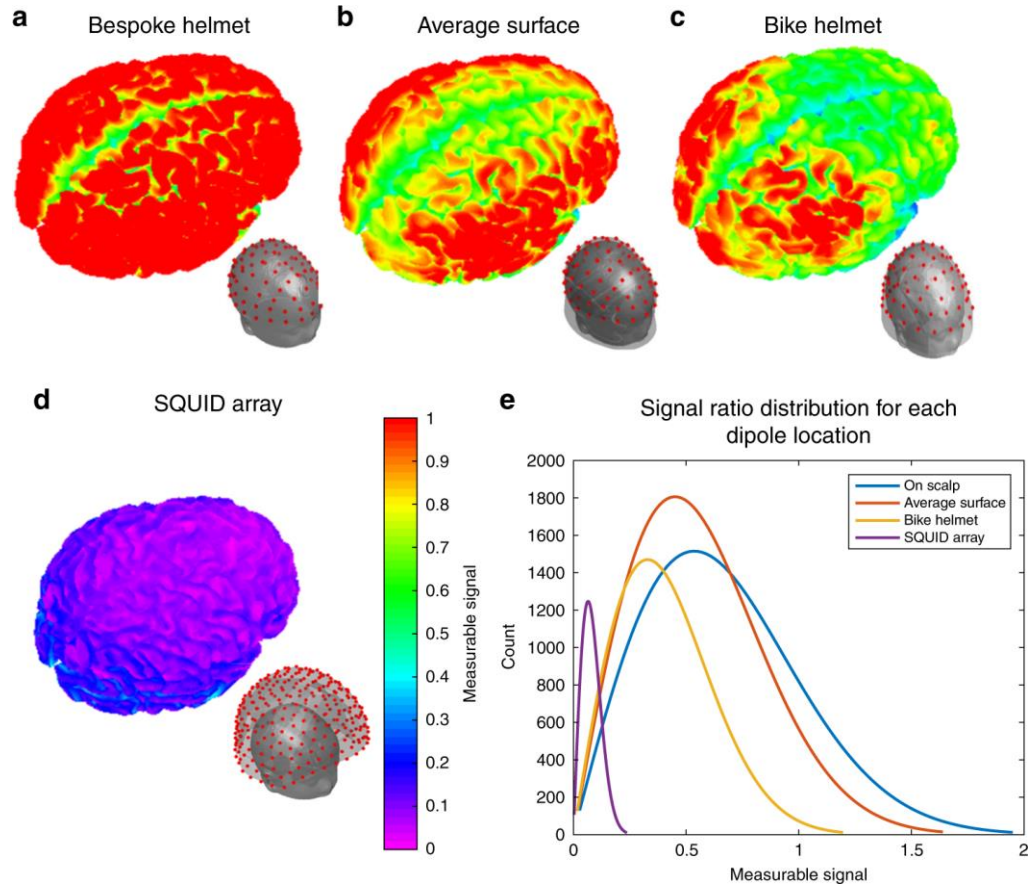


Figure 4.2: Simulated MEG helmet designs for a 2-year-old. Main figures show normalised representation of measurable signal across the brain. (Specifically a 1 nAm source dipole has been simulated at all cortical locations and we measured the Frobenius norm of the resulting sensor level field pattern. These values were normalised by the average Frobenius norm when sensors are placed on the scalp surface – i.e, the values, which mostly scale between 0 and 1, represent signal quality relative to the bespoke helmet). Inset figures show the location of simulated MEG sensors. A) Bespoke helmet. B) Helmet to fit 95% of 2-year-olds. C) Modified bike helmet. D) Cryogenic MEG system. E) Distribution of measurable signal values, across all dipole locations for each helmet type.

4.3 Temperature measurements

During normal operation each OPM cell is heated to 150 °C. Despite the sensor's thermal insulation, we wanted to ensure the temperature at the surface of the head was well controlled to ensure a safe scanning environment for the participant. The maximum temperature allowed to be in contact with a participant without first asking their permission is 41 °C, suggested by British Standards (BS EN 60601-1, 2000) (Medical electrical equipment. General requirements for safety. Collateral standard. Safety requirements for medical electrical systems). With the participant's permission, this allowance increases to 44°C. As another point of reference, ASTM C1055 (C1055-20, 2020) (the

Standard Guide for Heated System Surface Conditions that Produce Contact Burn Injuries)² recommends that the maximum contact temperature that will not cause burns over a 10-minute scan is ~48°C (although this is a device at a constant temperature, whereas the OPMs gradually heat over time). We also wanted to ensure that the OPMs did not stop working due to overheating while scanning. The sensors have a fail-safe software that switches off the sensor before it gets damaged, but the sensor must then be restarted and recalibrated before it can begin recording again. The thermal management of the sensors is especially important when the sensors are surrounded by the insulating polystyrene in the bike helmet.

Therefore, we performed temperature measurements in two setups: first, in a nylon 3D-printed scanner-cast design used in Boto et al. (Boto et al., 2018) to understand the thermal characteristics of the sensors in an already used system and to give us a system to compare to. Second, we repeated the measurements in the bike helmet to ensure that the temperatures did not behave drastically differently.

4.3.1 Nylon scanner-cast

Figure 4.3 shows the experimental set up for measuring the temperatures. An array of seven OPMs was housed within a scanner-cast. A thermocouple was placed directly on the central sensor to measure the temperature of the sensor surface (T1). A second thermocouple was placed on the inside of the scanner-cast, below the central sensor, to measure the temperature at the head (T2). Temperatures at both locations were recorded over a period of 10 minutes, whilst the array was worn by a participant. A nylon

² This standard provides the allowable skin-contact temperature as a function of time given by $T = 39.468 - 0.41352 \times \ln(t \times 1000) + \frac{190.60}{\ln(t \times 1000)}$, where t =time (in seconds) and T =temperature (in °C).

scanner-cast design was used with gaps in the side of the sensor slots for ventilation. In addition, pyrolytic graphite (Panasonic Corporation Japan) and a piece of 0.5-mm thick Nomex thermal insulating sheet (DuPont, US) were employed to dissipate heat out of the helmet and reduce the temperature at the head. Two experimental conditions were examined: 1) no insulation or pyrolytic graphite; 2) 3 insulating sheets and pyrolytic graphite wrapped over the tip and out of the scanner-cast (see Figure 4.3 C and D). The central sensor was alternated between each of the seven sensors in the array to check for inconsistencies between the sensors.

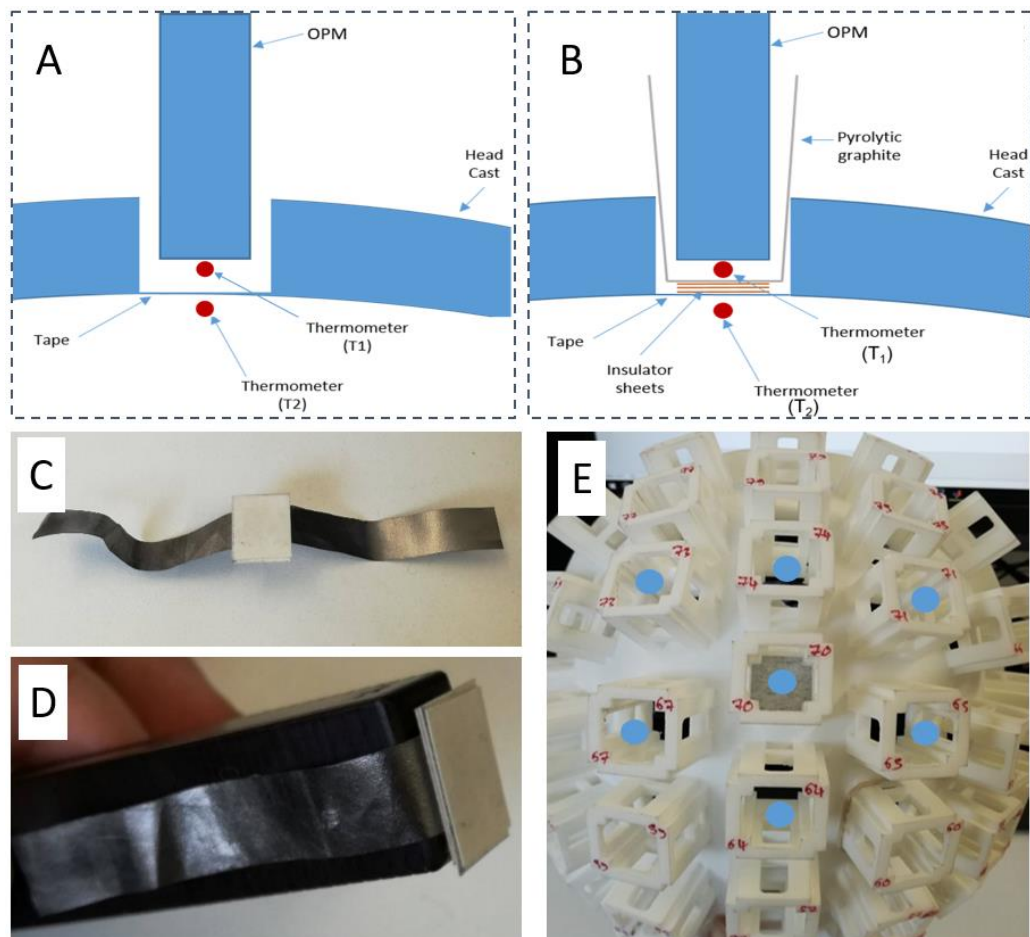


Figure 4.3: Set up for measuring central OPM surface (T_1) and head surface (T_2) temperatures. A) Case 1 Sensor is uncovered in the scanner cast. B) Case 2 Insulation and pyrolytic graphite are wrapped around the tip of all the sensors. C-D) Insulation and pyrolytic graphite. E) 7 sensors are housed in a scanner cast and are measured in the two cases.

Before performing measurements on a human head, we tested the uncontrolled setup (Figure 4.3A) using a polystyrene head to ensure the

sensors wouldn't burn the skin instantly on contact. After 10 minutes, the temperature at the head surface (T_2) reached 60 °C. This temperature would not instantly burn the skin on contact, but would become uncomfortable over longer periods of time. However, the polystyrene head also represents a worst case scenario as it provides extra insulation and no heat dispersion. In reality, the human head should conduct heat away. While the participant wore the helmet, they were able to continuously monitor the temperature to be aware of any excessive temperatures and could quickly remove the helmet (in a matter of seconds) if needed. Figure 4.4 shows the results from these experiments. A black dashed line at 41°C shows the maximum temperature allowed to be in contact with a participant without first asking their permission (BS EN (BSEN60601-1, 2000)).

With no insulation or pyrolytic graphite (case 1), the OPM surface temperature increased to 44°C after 10 minutes; the temperature on the head was 1.5 degrees lower than that at the sensor (42.5°C). Using insulating sheets and pyrolytic graphite (case 2), the sensor temperature was reduced to 42°C due to the pyrolytic graphite removing the heat from the scanner-cast. This coupled with extra insulation between the sensor casing and the head reduced the temperature on the head to 37°C. Repeating experiments across different sensors showed that results were independent of which sensor was used, with average temperatures of 38.4 ± 0.9 °C and 41.6 ± 1.5 °C measured at the surfaces of the head and the sensor respectively.

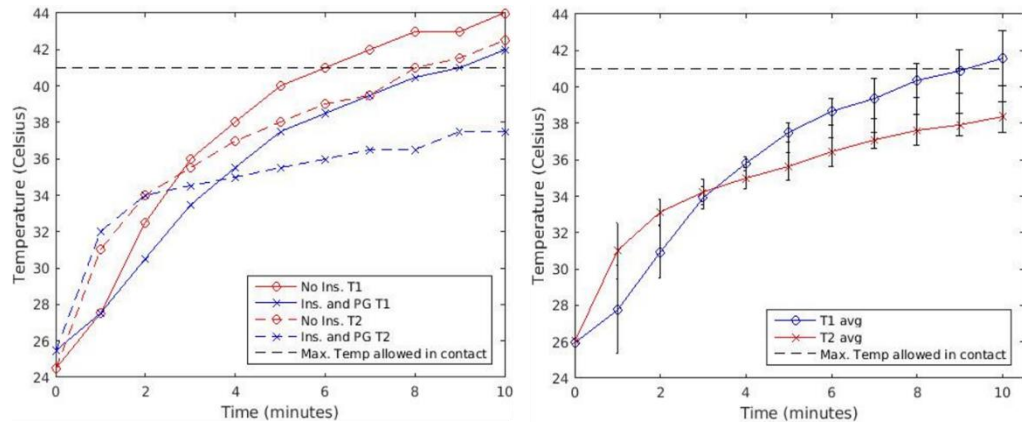


Figure 4.4: *Plots of temperature as a function of time. Black dashed line shows the maximum temperature allowed to be in contact with a subject without first warning them. Left) T1 and T2 temperatures over a 10-minute period of use for each case. Red lines show case 1 setup, and case 2 in blue. Solid lines are T1 temperatures and dashed lines are T2. Right) Average temperatures for all seven sensors when placed in turn at the centre of the array in the case 2 setup. Blue line shows T1 averages and red line shows T2.*

Clearly, the insulating sheet and the pyrolytic graphite have a dramatic effect at reducing both the temperature of the external surface of the OPMs and the temperature felt by the participant. The T2 temperature (i.e. the temperature that is felt at the participant's head) is at roughly body temperature meaning the sensors should be completely safe when using this setup (BSEN60601-1, 2000; C1055-20, 2020). Now that we have seen the effects in the scanner-cast setup, we must try the same experiments in the bike helmet to ensure we see a similar pattern.

4.3.2 Bike helmet temperature

Even though we have shown an effective temperature management method with the nylon scanner-cast, the polystyrene in the helmet will likely offer more insulation. However, the helmet also doesn't hold the sensors directly on the scalp (as it is a generic fit, not bespoke to the participant) which should reduce the temperature felt by the participant. We repeated the experiment described above but with the bike helmet in place of the scanner-cast, and only five sensors in the array. The sensors were laid out in the helmet as shown in Figure 4.5 (Left).

Chapter 4: Designing a generic OPM-MEG helmet

4.3 Temperature measurements

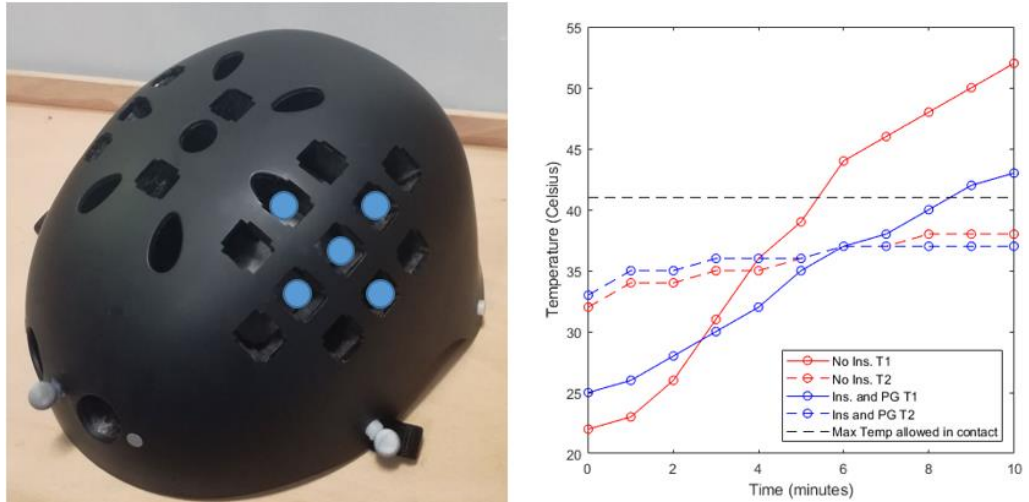


Figure 4.5: Setup and results for bike helmet temperature. Left: Sensor layout for measuring temperature. Temperature was measured underneath the central sensor. Right: Temperature measurements for the central sensor. Red shows the no insulation setup, and blue shows the insulation and pyrolytic graphite setup. Solid lines show the T1 (aka sensor) temperature, and the dashed lines show T2 (aka participant's head) temperature.

Figure 4.5 (Right) shows the results from these experiments. In the case with no insulation or pyrolytic graphite, the polystyrene of the inner bike helmet offers more insulation around the sensors causing them to reach much higher temperatures than when they are in the 3D printed head cast in section 4.3.1 (52 °C vs 44 °C respectively). However, because the sensors were not placed directly on the head, the T2 temperature was lower than in the 3D printed head cast with no insulation (38 °C vs 42 °C respectively). On adding the insulation and pyrolytic graphite, the temperature at the head remained roughly the same, while the sensor temperature was reduced to 43 °C.

In conclusion, using this thermal management technique we can keep the sensor temperature under control to prevent the sensors from overheating. Otherwise, the polystyrene insulation around the sensors could cause them to heat up too much and damage the internal components, or even worse injure the participant if an overheated sensor comes into contact with the scalp (but this is highly unlikely due to the fail-safe software).

4.4 Prototype helmet – designing coverage

At the time of designing the prototype, we had 12 Gen-1 QuSpin OPM sensors owned by the University of Nottingham and an additional 12 Gen-1 sensors on loan from our UCL collaborators (see Chapter 3 for a discussion on QuSpin OPM operation). Due to the limited number of sensors, we focussed on detecting beta-band modulation in the sensorimotor cortices at the expense of other brain regions. This is because our aim was to show a proof-of-principle prototype that could clearly detect these well documented responses that have been robustly observed in both adults and children (Liao et al., 2015; Pfurtscheller and Lopes da Silva, 1999). Therefore, in the design of the helmet, we needed to ensure the sensors were positioned for optimal coverage of the region of interest of the brain.

In order to compute the best location for the sensors in the helmet, a dipole was simulated at the centroid of the left sensorimotor cortex, identified using the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Further simulated dipoles were also placed within the same AAL parcel, with their magnitudes down-weighted in accordance with distance from the centroid. A forward field simulation (as above) projected a field pattern from these dipoles to the inner surface of the helmet, finding the optimal locations of slots within the helmet (see Figure 4.6).

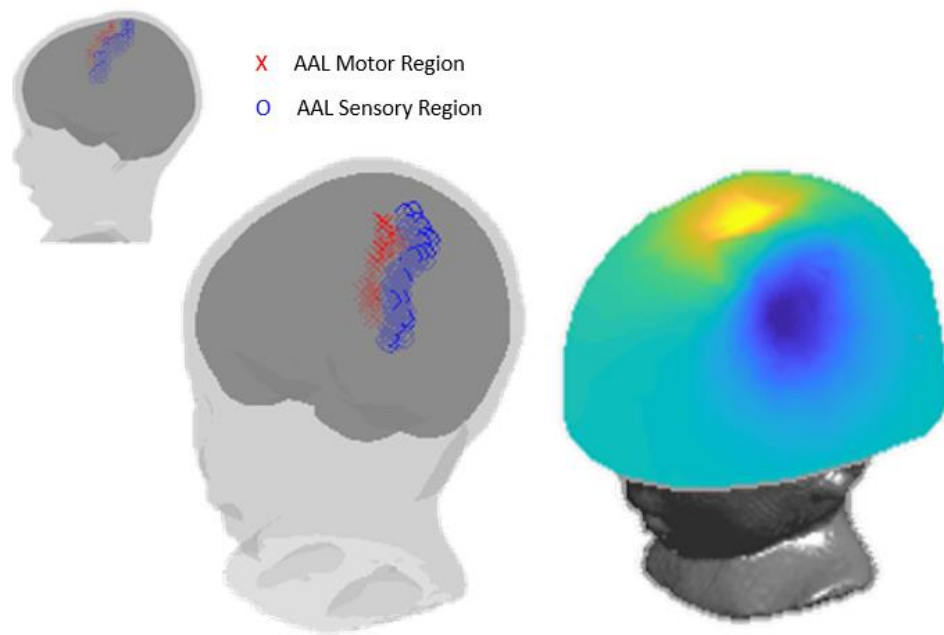


Figure 4.6: Forward field of left sensorimotor cortex. The forward field is calculated for a dipole placed at the centroid of the left sensorimotor region. Further dipoles are also simulated at each of the red and blue points, with their contribution down-weighted in accordance with their distance from the centroid. The field pattern is projected onto the inner surface of the bike helmet to give an estimation of the optimal sensor locations in the helmet. .

To simplify the data collection procedure, we took the decision to start with an adult helmet. An adult bike helmet was modified to securely house 24 Gen-1 QuSpin OPMs over the sensorimotor cortices, as well as having any magnetic components (such as press studs in the chin strap) removed. Each sensor was inserted so that the tip of the sensor was flush with the inner surface of the helmet. The helmet is thick enough to hold the sensors still and at a fixed orientation during scanning (see Figure 4.7).



Figure 4.7: Adult bike helmet. The modified adult bike helmet with sensors held in place with slots cut into the helmet. The thickness of the helmet allows the sensors to be held still and at a fixed orientation during scanning.

4.5 Co-registration

Having mounted the OPMs rigidly in the helmet, our next challenge is knowing where their sensing volumes are positioned in relation to the brain anatomy. This is critical if images showing source localised brain activity are to be derived, as even a co-registration error of a few millimetres is enough to detrimentally affect source reconstruction. In previous OPM-MEG systems, this problem was automatically solved by bespoke 3D printed head casts which provided accurate knowledge of the sensor locations and orientations to the participant's head. However, the generic nature of the bike helmet design means that this information is not known and varies for each participant. Here this problem was solved by developing a novel three-step process (see Figure 4.8):

- 1) A volumetric X-ray computed tomography (CT) scan of the bicycle helmet was acquired (Figure 4.8 A). Fake plastic OPMs were placed in the slots to show the sensor locations and orientations relative to the

helmet³. This provided a 3D digitised representation of the array, at a resolution of 162.9 μm . The plastic blocks have a different contrast in the CT image compared to helmet, which allowed the sensors to be identified using a simple thresholding technique. The locations were then manually identified and stored. From this digitisation, three reference points on the outer helmet surface were identified, and used to set up a co-ordinate system in which the locations and orientations of the sensors were set, relative to the helmet markers. Here, we have assumed that all OPMs are sensitive to the orientation perpendicular to the outer edge of the casing. However, the precise variation of the directional sensitivity from sensor to sensor is unknown and should be the topic of further work. This variation is a result of both the 3D printing error when creating the sensor casing, and cross-talk between the sensors. If the orientation is not accurately known, the forward field model will be incorrect and the beamformer will not produce the correct result.

- 2) Three IR retroreflective markers were placed on the helmet reference points. A further three were placed on a pair of glasses worn by the participant, which were fastened with a strap to reduce the movement during the scan (Figure 4.8 B and C). The two marker sets were treated as separate rigid bodies, and their translation and rotation monitored throughout the experiment using a motion tracking camera. This allowed knowledge of the location of the helmet relative to the glasses, and further allowed us to test whether the helmet moved during the scan.
- 3) Finally, the participant's head shape (scalp and face) was digitised using a 3D digitiser (Polhemus, Vermont, USA), in a coordinate system

³ We used fake OPMs as this was easier to transport to the CT scanning facility than taking the many thousands of pounds worth of sensors. Also, QuSpin ships the sensors to us with a big label saying "DO NOT X-RAY".

defined relative to the markers on the glasses (Figure 4.8 D). This allowed accurate knowledge of the location of the glasses relative to the head. The digitisation is then fitted to an anatomical MRI of the participant's head in order to perform source localisation.

Combining data from the CT scan (sensor locations relative to helmet markers), the motion tracking camera (helmet markers relative to the glasses), and the digitisation (glasses relative to the head) facilitated a complete co-registration of the location/orientation of the OPMs relative to the head. Note that mounting the fiducial markers on the head using a pair of glasses was a simple solution which worked well. However, a potential limitation is that the glasses may move during acquisition, or some people - especially children - might move them (or remove them completely). Crucially the only requirement is three retro-reflective markers at fiducial locations on the head. It is equally possible that these markers could be formed from three reflective stickers placed on the participant's face (we employ this strategy in Chapter 6.4).

The motion tracking camera is an OptiTrack V120:Duo camera (NaturalPoint Inc., Corvallis). It provides sub-1-millimetre and sub-1-degree precision optical tracking of a rigid body with a 120 Hz frame rate, using two cameras each with an array of 15 infra-red LEDs. The OptiTrack uses the Motive software platform to record and track infrared (IR) retroreflective markers. Additionally, the NatNet SDK software allowed control of the Motive software from a MATLAB script, enabling OptiTrack data to be synced to the MEG data.

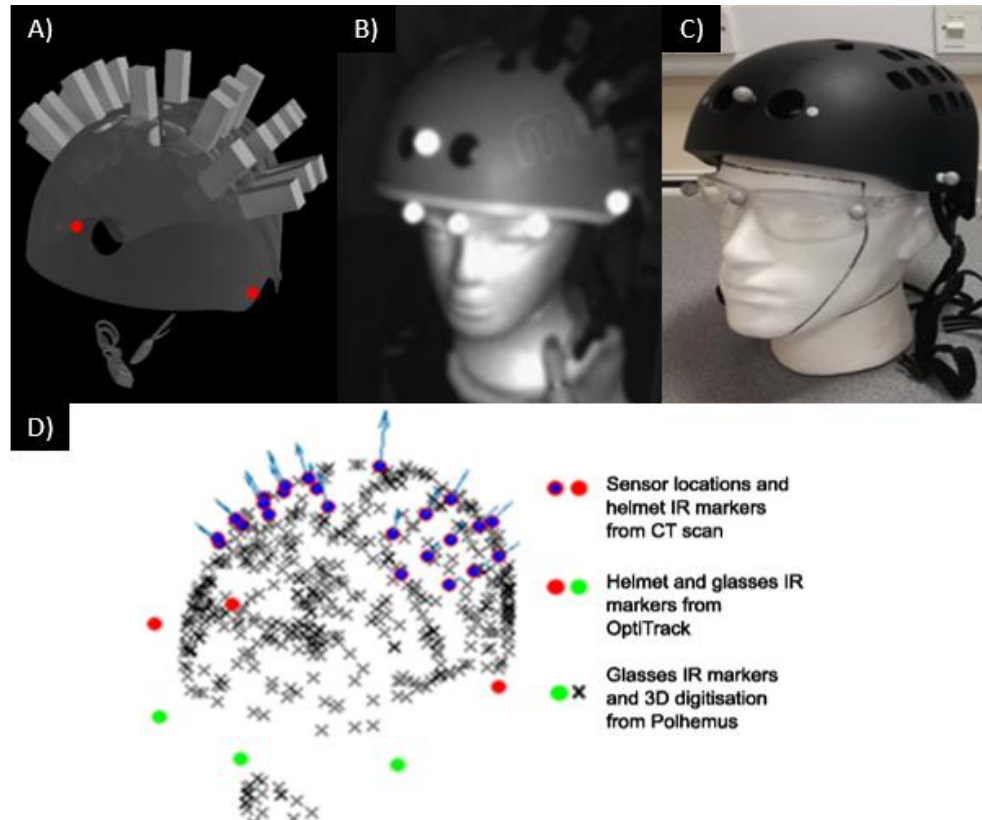


Figure 4.8: Co-registration process. A) A volumetric X-ray CT scan of the modified bicycle helmet. Note that the fake OPM sensor blocks have a different contrast to the helmet, allowing them to be identified using a thresholding technique. Three identifiable reference points on the outer helmet surface were chosen (red circles), one on the forehead, and the others above the left and right ears. These were later used to attach reflective markers visible to an IR tracking camera. B-C) A still from the motion tracking camera and a photograph of the modified bike helmet respectively. Note the three IR reflective markers attached to the surface. The participant also wears a pair of glasses, attached to which are a further three IR reflective markers, enabling co-registration of the helmet to the head. D) 3D digitisation of the participant's head shape, defined relative to the markers on the glasses (green circles). This digitisation has been aligned to the markers on the helmet (red circles) and OPM sensors (blue markers) to provide complete co-registration of the system to brain anatomy.

4.6 Experimental validation

To validate our helmet design, temperature control procedure, and co-registration procedure, three adults underwent a finger movement paradigm (similar to that described in Boto et al. (Boto et al., 2018)).

4.6.1 Methods

An overview of our complete system is shown in Figure 4.9. Data were recorded from the sensors at a sampling frequency of 1,200 Hz, using a 16-bit digital acquisition (DAQ) system comprising three NI-9205 modules, controlled

using custom-written software in LabVIEW (National Instruments). The sensors were housed in a three layer MSR (Vacuumschmelze) to reduce environmental interference, and bring the background static field down to approximately 30 nT; all control equipment was kept outside the room.

In order to enable free head movement during scanning, it is necessary to null any residual static (i.e. Earth's) magnetic field inside the MSR (Boto et al., 2018; Holmes et al., 2018). In the absence of such nulling, any movement of the sensors with respect to the background field will cause large artefacts (enough to send the sensors outside their dynamic range). In fact, a 30 nT static field means that a head rotation of just 3° is enough to generate a 1.5 nT field change, which would in turn cause a significant (>5%) change in gain of the OPM, as discussed in Chapter 3. To achieve this nulling, prior to data acquisition (but with the participant in place) we used a reference array to measure the ambient static field, and its three most prominent gradients⁴. This information was fed into a control algorithm which outputs currents through an array of six electromagnetic coils (Holmes et al., 2018) placed either side of the participant. These currents were held for the duration of the experiment (i.e. they were not constantly updated to provide dynamic nulling). The resulting magnetic fields from these coils cancelled the static magnetic field inside the MSR. During data acquisition, both the head array and the reference sensors were operated simultaneously. Throughout the scan, stimulus delivery was controlled by a separate computer (running MATLAB) which also provided temporal markers to the acquisition computer.

Three participants (2 males, aged 24 and 28 years, and one female aged 27 years, all right handed) took part in the study. All three participants provided

⁴ The reference array described here was used for nulling purposes only in all experiments in this thesis, not for synthetic gradiometry purposes as in commercial cryogenic systems described in Chapter 2, Section 3.2.1.

written informed consent and the study was approved by the University of Nottingham Medical School Ethics committee. Participants were seated but allowed to move freely. Visual cues to the participant were projected through a waveguide in the wall of the MSR onto a back-projection screen which was positioned ~40 cm in front of the participant.

A grating appeared for 2 s, followed by a 3 s rest with a fixation cross shown throughout. During presentation of the grating, the participant was instructed to perform repeated abductions of their right (dominant) index finger, and to stop once the grating disappeared. Using this paradigm, we expect to see a decrease in beta amplitude (beta desynchronisation) during the 2-s finger abduction, followed by an increase in beta amplitude above baseline (beta rebound) at the cessation of movement, before returning to rest amplitude. 100 trials were undertaken.

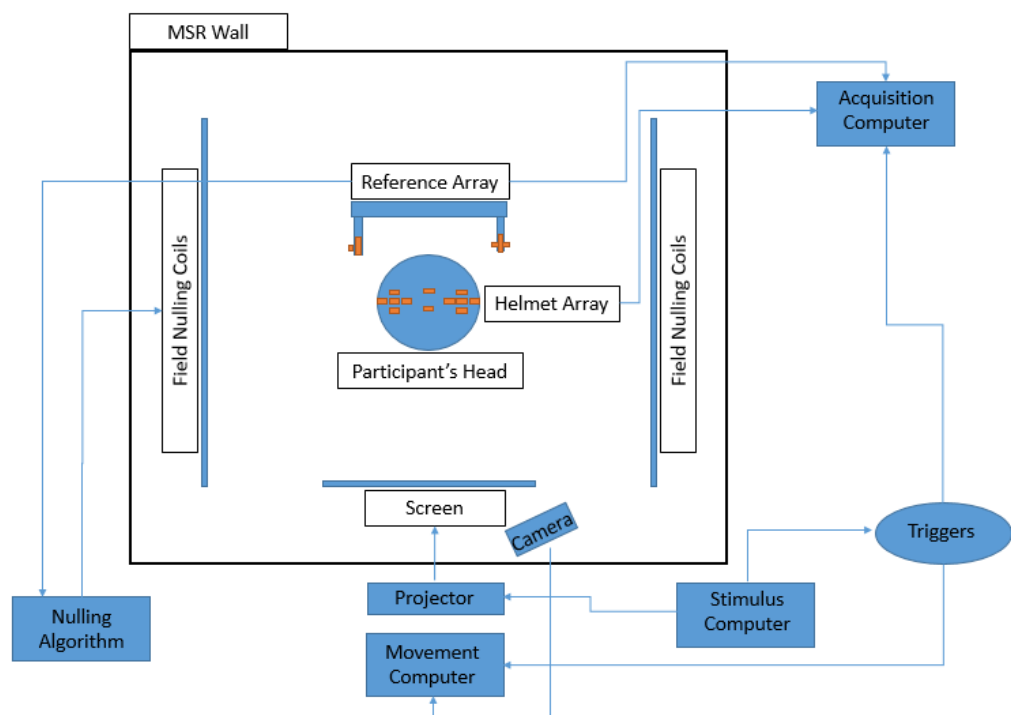


Figure 4.9: Schematic overview of the OPM-MEG system.

Data were inspected visually to check for and remove excessive interference. At the channel level we used a pseudo-gradiometer⁵ approach in which signals from neighbouring magnetometer sensors were subtracted (see Figure 4.10). In doing this, fields that originate directly below the gradiometer pair are enhanced, while signals from elsewhere are reduced (see Chapter 2.3.2). Such a technique is required as the magnetometers are more susceptible to noise than the hardwired gradiometers in commercial cryogenic systems, which can obscure neurological effects. As we are scanning participants that are free to move during the experiment, the motion artefact (the signal produced as a participant moves through a magnetic field) is the dominant source of noise. This typically occurs at <10 Hz, and is similar enough in profile across nearest neighbour sensors to be effectively removed by the pseudo-gradiometers.

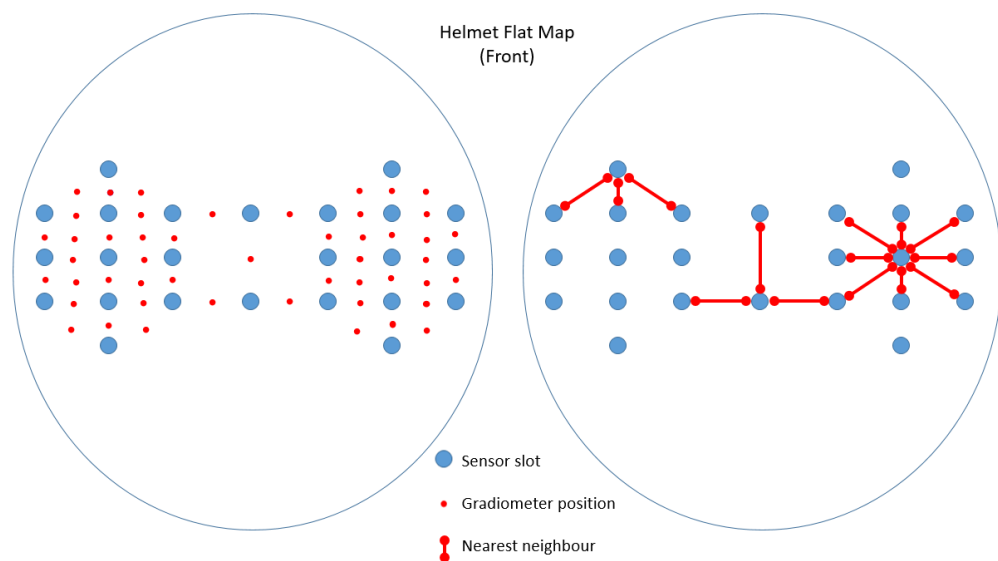


Figure 4.10: Nearest neighbour selection. In order to create the pseudo-gradiometers, we subtracted the signals from nearest neighbour magnetometers. The blue dots show the slot positions, the red dots the positions of the pseudo-gradiometers (found by taking the mean of the slot locations), and the red connectors give examples of how nearest neighbours were determined

⁵ Here, we use the term pseudo-gradiometer as they are not hardwired together as described in Chapter 2 for the SQUIDS. Instead, they are formed by the subtraction of two separate magnetometers.

For source localisation we used a beamformer approach (described in Chapter 2). The forward field vector, $\mathbf{L}_\theta$, is modified to account for the gradiometer pairs used to generate $\mathbf{m}(t)$ by first calculating the lead fields at each sensor location, then subtracting the lead fields for each sensor pair (e.g. the lead field for a gradiometer pair formed by sensor i and sensor j is found by subtracting the lead field at sensor j from the lead field at sensor i , i.e. $L_{ij} = L_i - L_j$). Weights were determined using data covariance measured in beta band filtered (13-30 Hz) data, and using a time window capturing the entire experiment. The regularisation parameter was set to 0.05 times the maximum eigenvalue of the un-regularised matrix. The forward field was computed using a simple spherical head model and the dipole approximation first described by Sarvas (Sarvas, 1987). In order to generate images of the spatial signature of beta modulation, two further covariance matrices were defined: C_a represents data covariance in the active window ($0 \text{ s} < t < 2 \text{ s}$ relative to trial onset, the period of finger movement). C_c represents data covariance in the control window ($3 \text{ s} < t < 5 \text{ s}$, the period of rest). A pseudo-T-statistical contrast, given by

$$T_\theta = \frac{\mathbf{w}_\theta^T C_a \mathbf{w}_\theta - \mathbf{w}_\theta^T C_c \mathbf{w}_\theta}{2 \mathbf{w}_\theta^T C_c \mathbf{w}_\theta}, \quad [4.2]$$

was computed at the vertices of a regular 4-mm grid spanning the whole brain to generate the functional images. Note that the orientation of the source in each voxel was determined as that which gave the maximum signal-to-noise ratio.

Based on the pseudo-t-statistical images, a peak location was determined, and a signal from this location was reconstructed. Using data covariance calculated in the broad (1–150 Hz) band, beamformer weights were used to generate a broad-band ‘virtual sensor’ time course. A time-frequency spectrogram was then constructed by sequentially frequency filtering the

signal into overlapping bands, computing the envelope of oscillatory power, averaging over trials and concatenating in the frequency dimension.

We also test the localisation accuracy using the Harvard–Oxford Atlas. This atlas is based on the Montreal Neurological Institute (MNI) 152 standard brain, which is formed by averaging together 152 structural images. T1-weighted images of 37 healthy subjects were individually segmented into 48 cortical and 21 subcortical structural areas before being affine-registered to the MNI152 standard brain. This transform was then applied to the individual brain region labels for each subject, and then combined across subjects to form population probability maps for each label. By performing an affine-registration of the anatomical MRI images for each of our participants to the MNI152 standard brain, we can obtain MNI coordinates for the peak location of the beta response, and in turn find the most probable region of the brain the MNI coordinates correspond to according to the Harvard-Oxford Atlas.

4.6.2 Results

Results are shown in Figure 4.11. Note that, despite relatively sparse sensor coverage, beta modulation was well localised to contralateral motor cortex. Quantitatively, the peaks in the beta response were found at MNI coordinates (-44 -16 56) mm, (-36 -22 48) mm and, (-42 -6 52) mm for the three participants. According to the Harvard-Oxford probabilistic atlas, all three coordinates fall in precentral gyrus (with probabilities of 41%, 43%, and 70% respectively), as would be expected for a motor response. In addition, all three participants' reconstructed data show the expected beta-band modulation with a clear movement related beta decrease during movement and post movement rebound on movement cessation.

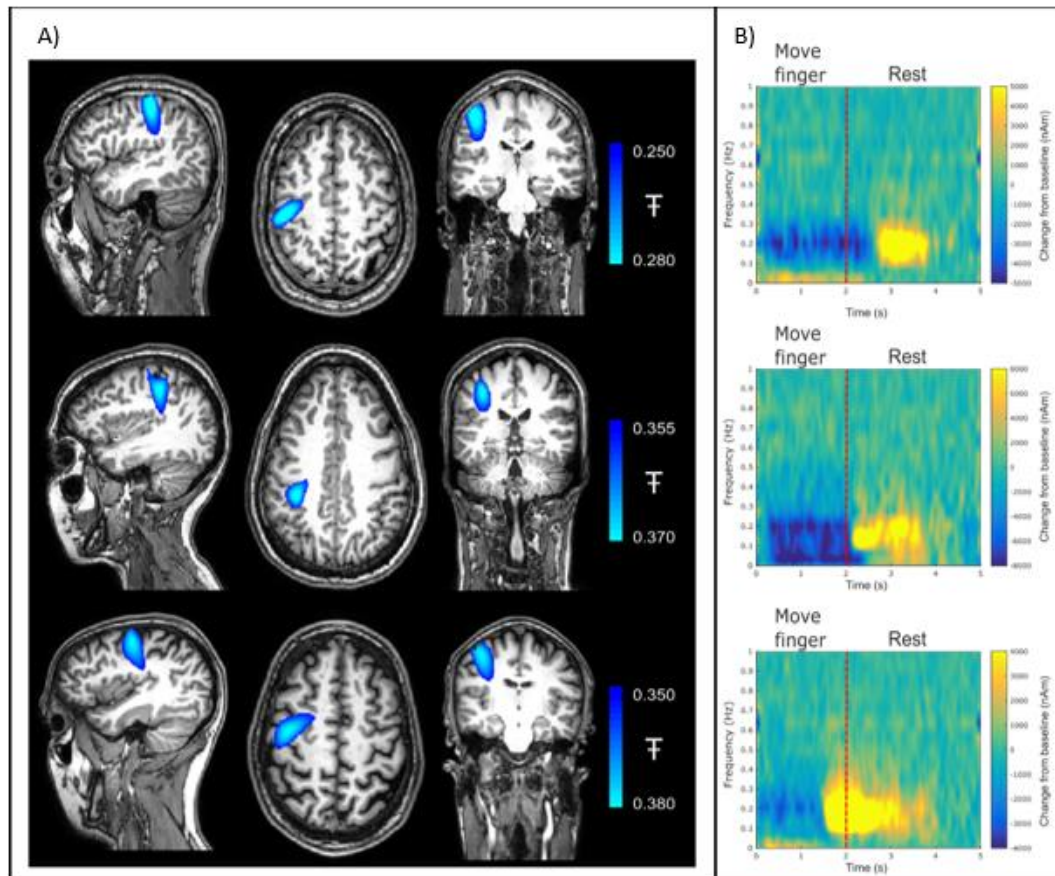


Figure 4.11: Co-registration validation. A) Images showing the spatial signature of beta modulation; the largest peak was found in pre-central-sulcus (motor cortex) in all 3 subjects. B) Time frequency spectra, reconstructed using a beamformer at the location of maximum beta change (i.e. the peaks in A).

4.7 Discussion

This chapter has described the design and initial implementation of a generic OPM-MEG system. Using simulations we demonstrated that a simple, modified bicycle helmet offered a good compromise between high signal strength (getting sensors as close as possible to the head), and a practical and ergonomic design that could be deployed across all ages. Children are familiar with bike helmets and should therefore not be as daunted by wearing them during an experiment. We also undertook experiments to ensure that the temperatures of the sensors are controlled using a combination of pyrolytic graphite (to conduct the heat out of the helmet) and thermally insulating sheets (to prevent the heat being conducted to the scalp). This is important for two reasons: 1) to prevent the sensors from rebooting due to overheating, and 2) prevent the participant from being injured or getting too uncomfortable

during scanning. By introduction of a technique for co-registration between sensor locations and brain anatomy, we were able to generate 3-dimensional images of the spatial signature of changes in neural oscillations as three participants performed a finger abduction. We then validated this localisation using the Harvard-Oxford atlas which showed the activity was well localised to the pre-central-gyrus, as would be expected for a motor response. In an ideal situation, it would have been better to elicit responses in various brain regions and ensure the co-registration accurately reconstructed the activity in appropriate regions. However, due to the number of sensors available, we limited ourselves to the motor cortex responses, and so the Harvard-Oxford atlas provided the most appropriate practical validation.

Unlike static systems shown in Iivanainen et al. (Iivanainen et al., 2019c) and Borna et al. (Borna et al., 2017), the bike helmet is wearable which allows for participant movement, providing appropriate field nulling techniques are used. Boto et al. (Boto et al., 2018) and Holmes et al. (Holmes et al., 2018) also demonstrate this ability but they rely on bespoke 3D printed scanner-casts, which increase the cost of scanning, particularly for large cohorts. They are also too heavy and somewhat intimidating for children to wear. By replacing them with a generic bike helmet, it's possible to scan multiple people with the same setup, at a much reduced cost, and with a more friendly and ergonomic design. Such a system would allow us to study brain function across the lifespan and across large cohorts with greater ease.

Now that we have demonstrated the validity of this prototype generic system for adults, we aim to explore the application to multiple age groups in order to create a true generic system with lifetime compliance. This work is discussed in Chapter 5.

Chapter 5: Demonstrating lifespan compliance

Following the simulation, design, and experimental validation of a helmet for lifespan imaging, we now explore its application in multiple age groups. Here, we use three paradigms that each elicit beta band modulation. We first demonstrate a sensory maternal touch task in 2-, 5-, and 24-year-old participants. Second, we demonstrate a variation on a ballistic finger movement paradigm in a 14-year-old participant, where the participant is prompted by playing a computer game rather than a standard visual cue. Finally, we use a natural motor learning paradigm as a 24-year-old participant plays a musical instrument. In all three experiments, we see the expected beta desynchronisation signature across all participants, showing that lifespan imaging is possible with an OPM-MEG system. The results presented here have been published in Hill et al., Nature Communications (Hill et al., 2019).

5.1 Introduction

In Chapter 4, we designed and fabricated a generic OPM-MEG system using a modified bike helmet. This design offered a good compromise between high signal strength (getting sensors as close as possible to the head), and a practical and ergonomic design that could, in principle, be deployed across all ages. Extensive testing and modification with pyrolytic graphite and insulation showed that this system was safe to use and OPMs would operate at controlled temperatures. From an ergonomic point of view, the bike helmet is a familiar sight to children so would be less intimidating than the 3D printed prototypes used in Boto et al. (Boto et al., 2018). We also devised a co-registration technique and validated the technique on three adult participants using a finger abduction task. Even though we successfully localised movement induced beta fluctuations, the three adult participants were experienced subjects for MEG (both cryogenic and OPM) and so, while they were not constrained, they were not instructed to move and performed very little head motion throughout the experiment. With a child participant, this would almost certainly not be the case.

In this chapter, we extend this work by aiming to show that it is possible to detect high fidelity MEG signals even when individuals perform natural head movement during a task, as well as to confirm that our system can be tolerated by a child. In this chapter, we detail three experiments. The first is a maternal touch paradigm in two children ages 2- and 5-years-old as well as in a 24-year-old adult. This stimulus, which involves sensory stimulation by stroking the palm of the hand, is relatively simple and easy to carry out (an especially important requirement when trying to scan young children) but is still able to elicit a powerful sensory response. The second is an interactive motor paradigm in a 14-year-old participant that turns a typical ballistic finger movement paradigm into a “Robin Hood” themed computer game. The paradigm is controlled by movement of the finger, and the game provides real-time feedback to the participant to keep them engaged. Finally, we perform a

naturalistic motor learning task (where the participant must play a musical instrument) in a 24-year-old participant. This fully exploits the motion robustness of OPM-MEG, and ensures that a generic system can be used in this way. By being able to perform such a task, it would open up the possibility of new motor learning paradigms that we have so far been unable to explore due to movement restrictions (we further this work in Chapter 8).

5.2 Methods

We designed three paradigms that aim to adapt to increasing age ranges so that they are suitably engaging for the participants whilst being practical and relatively simple to perform.

5.2.1 Maternal touch paradigm

We first aimed to test the feasibility of our approach by recording brain activity in response to maternal touch in children aged 2 and 5 years (both male). Twelve OPMs (QuSpin Inc.) were mounted bilaterally above the somatosensory cortex in a modified children's bicycle helmet (instead of the adult helmet shown in Chapter 4). This design was well tolerated by the children. Indeed, the children had the opportunity to wear the helmet at home before the scanning session and even to wear a replica on a bike ride, in order to familiarise themselves with the helmet and reduce anxiety during scanning.

OPM-MEG data were recorded during a sensory task, in which the child's mother gently stroked the thenar eminence on the palm of the hand with a soft brush. Stimulation for 2 s was followed by 3 s rest in 50 trials, across which data were averaged. We expect to observe a reduction in the mu/beta amplitude during the 'On' period.

The children watched a television programme throughout. The video was displayed onto the projection screen, and the audio was played through

speakers that were placed against the waveguide on the outside of the MSR⁶. This helped to keep the children relaxed and entertained during the scan. It also helped to keep the children seated in the chair as the system, which can tolerate reasonably large movements, cannot tolerate a child getting up and walking off (yet). An LED mounted on the wall cued the mother to stroke the child's hand. The onset of the stimulation depends on the reaction time from the mother in response to the LED cue. Therefore, we are not able to study an evoked response, but we can observe the induced beta-band response. An adult (male, aged 24) was also scanned using the same task (and a larger helmet), with an experimenter stroking their hand. Movement of the head was tracked using the OptiTrack camera.

5.2.2 An interactive motor paradigm (Robin Hood)

Next, we aimed to show that the same system could be used in older children, alongside a naturalistic (and engaging) motor paradigm. One participant (female aged 14, right handed) took part in the study. The participant played a game in which a crosshair moved smoothly over a series of ten targets, and the participant shot arrows by moving their right index finger. When a shot was fired the position of the arrow was recorded as a black marker on the screen, and the participant was able to score points by hitting the targets (see Figure 5.1).

⁶ In order for the audio to be loud enough inside the room, the speakers had to be very loud outside of the room. I now have a deep hatred for the "Justin Time" theme tune after hearing it on repeat at very high volumes for several hours...

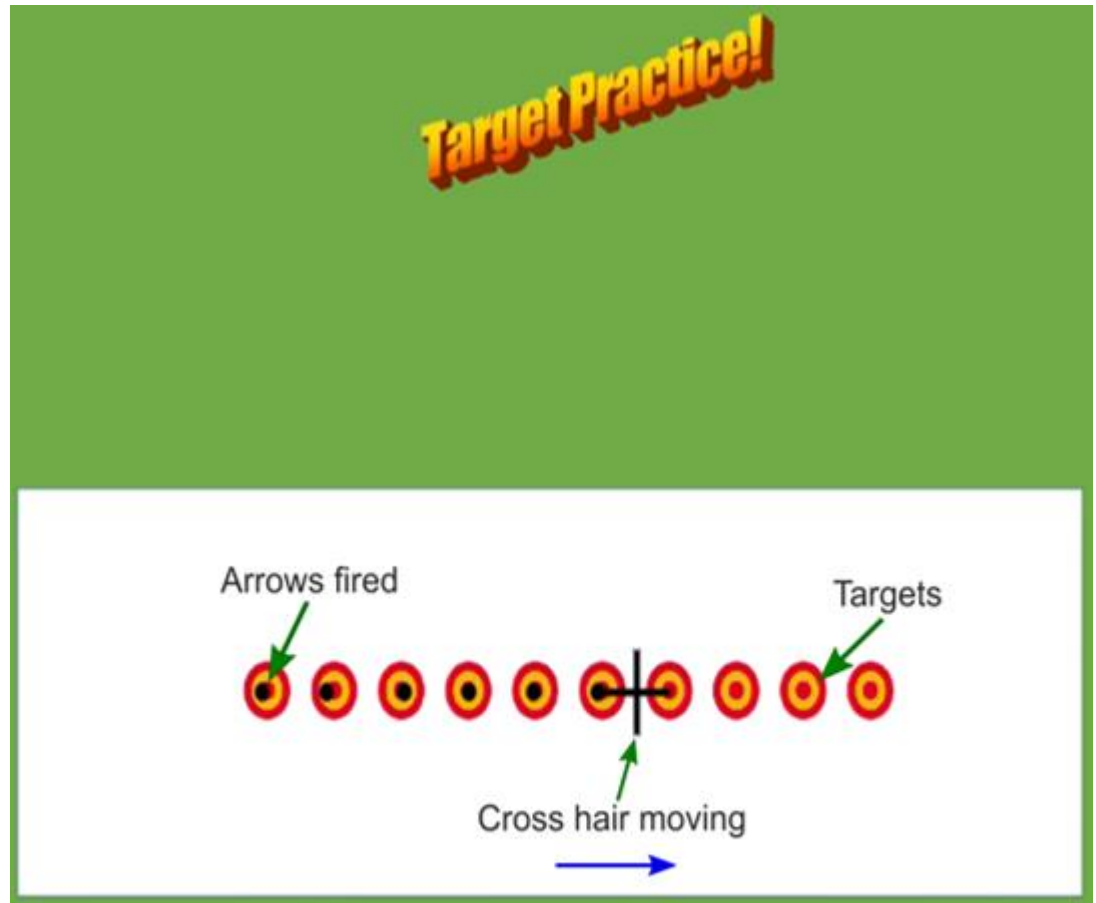


Figure 5.1: Robin Hood paradigm. A cross hair moves across the screen passing targets. The participant moves their finger in order to shoot an arrow at the target.

We determine whether arrows were fired (i.e. the index finger was moved) by tracking the finger with the OptiTrack camera described in Chapter 4.5. In order to do this in real-time, we used the NatNet SDK software to control the Motive software (which controls the OptiTrack) from a MATLAB script, enabling the OptiTrack data to be synced to the MEG data. The NatNet software also allows marker information to be simultaneously streamed (at a sample rate of 120 Hz) to MATLAB to control paradigms. By continuously monitoring the motion of an IR retroreflective marker placed on the finger, any time the finger moved, a trigger was sent to the DAQ and a black marker was shown on the screen. Finger movement was determined by taking the standard deviation of the finger trace over a 5-point window (e.g. if the current time point is x , the standard deviation of $[x - 5, x - 4, \dots, x]$ is found). When the

standard deviation of this window exceeded a threshold value⁷, this counted as a finger movement.

The speed of the crosshair changed throughout the experiment to alter the difficulty, with a slow trial taking approximately 5 s for the cross hair to move across the screen, and a fast trial taking approximately 3 s.

Each trial was followed by 10 s of rest. Here, we expected to see the same beta band modulation shown in Chapter 4.6. There was a total of 30 trials split into three blocks of ten, with a 40 s rest period between each block. 8 OPMs were placed over the left sensorimotor cortex to measure the response from the right finger movement. We synchronised data analysis (time $t = 0$) to the measured offset of motion.

5.2.2.1 Dealing with dental braces

The participant for this experiment also had dental braces. This is likely a contraindication to conventional MEG because even small amounts of head movement relative to a fixed (cryogenic) sensor array would cause large artefacts due to the metal of the braces. However for OPM-MEG, since the braces are fixed in the same frame of reference as the sensors, this was not considered a problem. However to accommodate this, the field nulling process was adapted. The background field was separated into two components: the remnant Earth's field in the room, $\mathbf{B}_E$, and the field due to the braces, $\mathbf{B}_B$. $\mathbf{B}_E$ is spatially locked to the MSR, whereas $\mathbf{B}_B$ is locked to the head, therefore in the reference frame of the OPMs only $\mathbf{B}_E$ changes with time if the head moves. Field nulling was therefore applied without the participant in the room, to null $\mathbf{B}_E$.

⁷ This value was arbitrarily chosen to ensure the game wasn't too sensitive to small finger movements that weren't intended by the participant. It was chosen by doing some test runs before beginning the experiment to find a comfortable setting.

Once the participant is brought in, the on-board-sensor coils were used to null B_B .

5.2.3 Naturalistic motor learning (ukulele)

As a final demonstration of the versatility of our system we aimed to scan an adult executing a naturalistic task. One participant (female aged 24, right handed) took part in an experiment where she was asked to play a musical instrument. Specifically, she was asked to learn to play a sequence of five chords (C, F, G, C, G) on a ukulele (shown in Figure 5.2 (Top)). These chords were selected as they progress through using 1, 2 and 3 fingers at a time⁸. The chords were visually projected onto a screen, and she was given 5 s to complete the sequence, with a 10-s rest after each attempt. Once again, we expected to see the beta desynchronisation/rebound pattern seen in Chapter 4.6. This was repeated 40 times. 8 OPMs were placed over the left sensorimotor cortex to measure the response from the strumming (i.e. right hand) movement.

The OptiTrack camera measured the head movement, as well as movement of the strumming hand by attaching an IR retroreflective marker around the thumb. An audio signal (from a microphone in the MSR) was also recorded. The Ukulele was modified slightly to remove metal components (including the tuning pegs, which were replaced with plastic friction pegs, similar to those found on a violin) (Figure 5.2 (Bottom)).

⁸ They also have the added bonus of being the most commonly used ukulele chords in pop music.

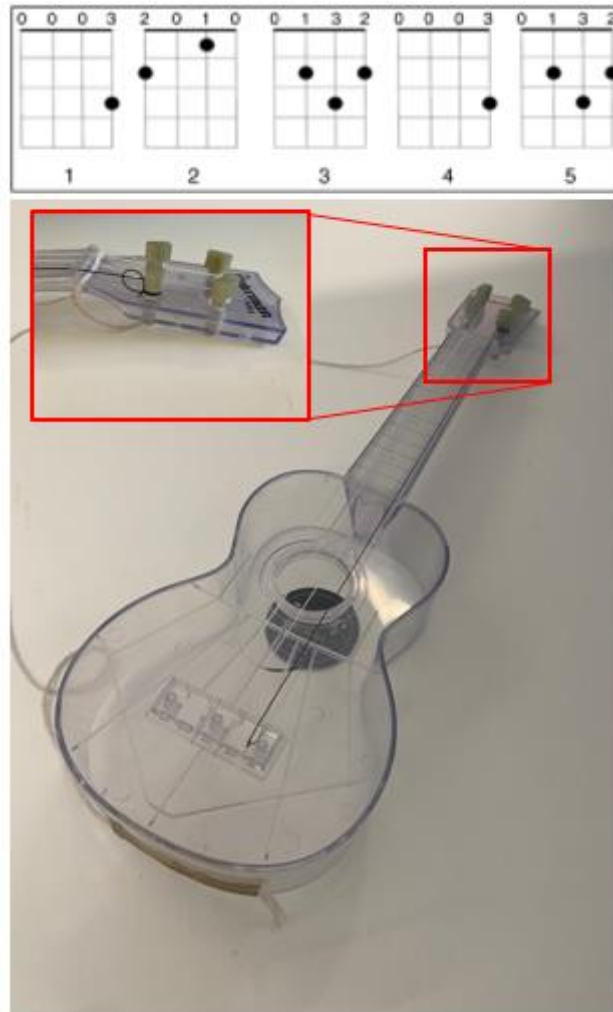


Figure 5.2: Ukulele chords. (Top) The five chord sequence used in the paradigm. The sequence is C F G C G. (Bottom) The plastic ukulele. I wouldn't gig with it any time soon.

5.2.4 Data acquisition

An overview of the system is shown in Figure 5.3 (Left). The system is identical to the one described in Chapter 4.6, other than the LED cue on the wall.

In addition to the adult sized bike helmet from Chapter 4, a second smaller child's helmet was modified in a similar way. However, because the child's helmet was smaller, supporting blocks were screwed to the surface of the helmet and the OPMs secured to these blocks to stabilise them (Figure 5.3 (Right)). A volumetric X-ray CT scan was also performed for this helmet in order to use the same co-registration procedure described in Chapter 4.5.

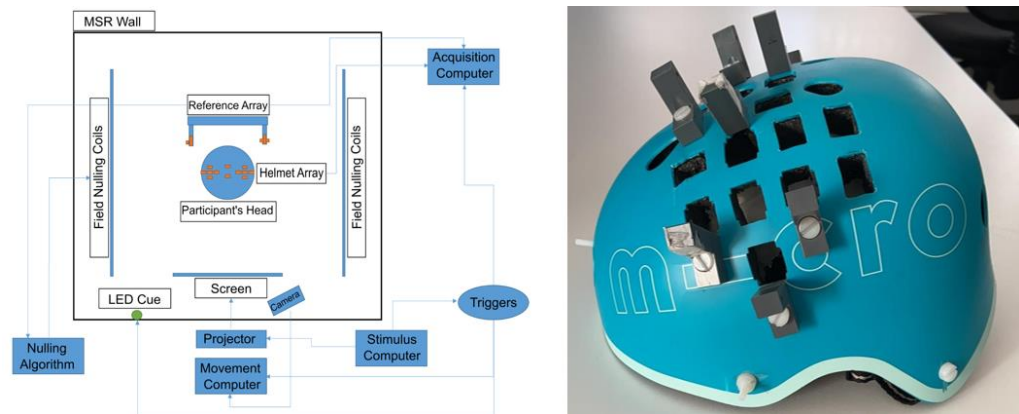


Figure 5.3: Experimental setup. (Left) Schematic overview of the OPM-MEG system. Identical to the setup described in Chapter 4 aside from the LED cue on the wall. (Right) Children's bike helmet with struts to hold the sensors more rigidly.

5.2.5 Data analysis

Data were inspected visually to check for and remove excessive interference. Data from two of the OPMs for the 2-year-old participant were removed. These sensors had less opaque packaging and the OptiTrack camera's infrared LEDs produced interference on the sensor's outputs. These two sensors were replaced in later experiments.

We used sensor space (gradiometer⁹) data to generate time frequency spectrograms (TFSs). To this end, the raw neuromagnetic signal was frequency filtered into overlapping frequency bands. A Hilbert transform generated the amplitude envelope of oscillations within each band. The envelope time courses were then averaged across trials, and concatenated in frequency to form a TFS showing change in oscillatory amplitude over time. For the maternal touch and Robin Hood paradigms, the TFS shows absolute change in oscillatory amplitude from baseline, in units of fT (i.e. a baseline oscillatory amplitude was defined, individually for every frequency band, in the 3.5–4.5 s window (maternal touch task) or the 1–3 s window (Robin Hood task)). These values

⁹ Gradiometers were formed by using nearest neighbour pairs as described in Chapter 4.6.

were then subtracted from the TFS to leave a measure of absolute oscillatory amplitude change relative to baseline. For the ukulele task, in order to highlight changes in gamma activity, we present relative change in oscillatory power. Here, the baseline amplitude was defined for all bands in the 9–14 s window; this was then subtracted from the TFS, and the result divided by the same baseline, yielding a fractional measurement.

In order to generate the images showing the cortical origin of the beta band effect in the maternal touch paradigm, accurate information on the locations and orientations of the sensors relative to the brain is required. This problem was solved using the method described in Chapter 4.5. For the 24-year-old participant, the anatomical image was acquired using a 3T MRI scanner running an MPRAGE (Brant-Zawadzki, 1992) sequence, at an isotropic spatial resolution of 1 mm. However, for the children, we adopted a pseudo-MRI approach (Holliday, 2003) whereby an existing MRI from a database was used instead of the participant's own data. Images were selected from a database containing MRIs of children in the same age group based on a best matching head shape (found using an iterative closest point algorithm).

A beamformer technique (Robinson and Vrba, 1998) as described in Chapter 2.2 was then used to localise sources of beta modulation. The regularisation parameter was set to 0.05 times the maximum eigenvalue of the un-regularised matrix, and the active covariance and contrast windows were taken at $0\text{ s} < t < 2\text{ s}$ and $3\text{ s} < t < 5\text{ s}$ respectively. We did not perform source localisation for the Robin Hood or Ukulele tasks as there were even fewer sensors available and they were all located over a single hemisphere.

5.2.6 Other

All participants provided written informed consent for all experiments. For participants under 18 years old, consent was given by their parents. All

studies were approved by the University of Nottingham Medical School Ethics Committee. Participants were seated but allowed to move freely (the 2-year-old sat on his mum's knee (shown in Figure 5.4)). Any visual cues to the participant were projected through a waveguide in the wall of the MSR onto a back-projection screen which was positioned ~40 cm in front of the participant.



Figure 5.4: 2-year-old sat on his mother's knee. The cutest image in the entire thesis (also note the chocolate bribe). Permission for the use of this photo was granted by the mother.

5.3 Results

5.3.1 Maternal touch

The maximum head translations/rotations tracked by the OptiTrack camera were 2cm/6°, 2.5cm/13° and 2cm/6° for the 2-, 5- and 24-year-old, respectively. These movements are within the maximum translations shown in Boto et al. (Boto et al., 2018) (maximum translations of 10 cm) but are large when compared to the 5-mm tolerance in cryogenic MEG.

The helmet setup for each participant is shown in Figure 5.5a. Clear changes in brain activity were recorded in response to stimulation using synthesised gradiometers, formed in the same way as described in Chapter 4.6 (Figure 5.5b). A reduction in the mu/beta amplitude was observed during stimulation in all three participants, as would be expected (Liao et al., 2015; Pfurtscheller and Lopes da Silva, 1999). Following co-registration and beamforming, the largest change in beta activity was identified in the contralateral primary somatosensory cortex in all participants (see Figure 5.5c).

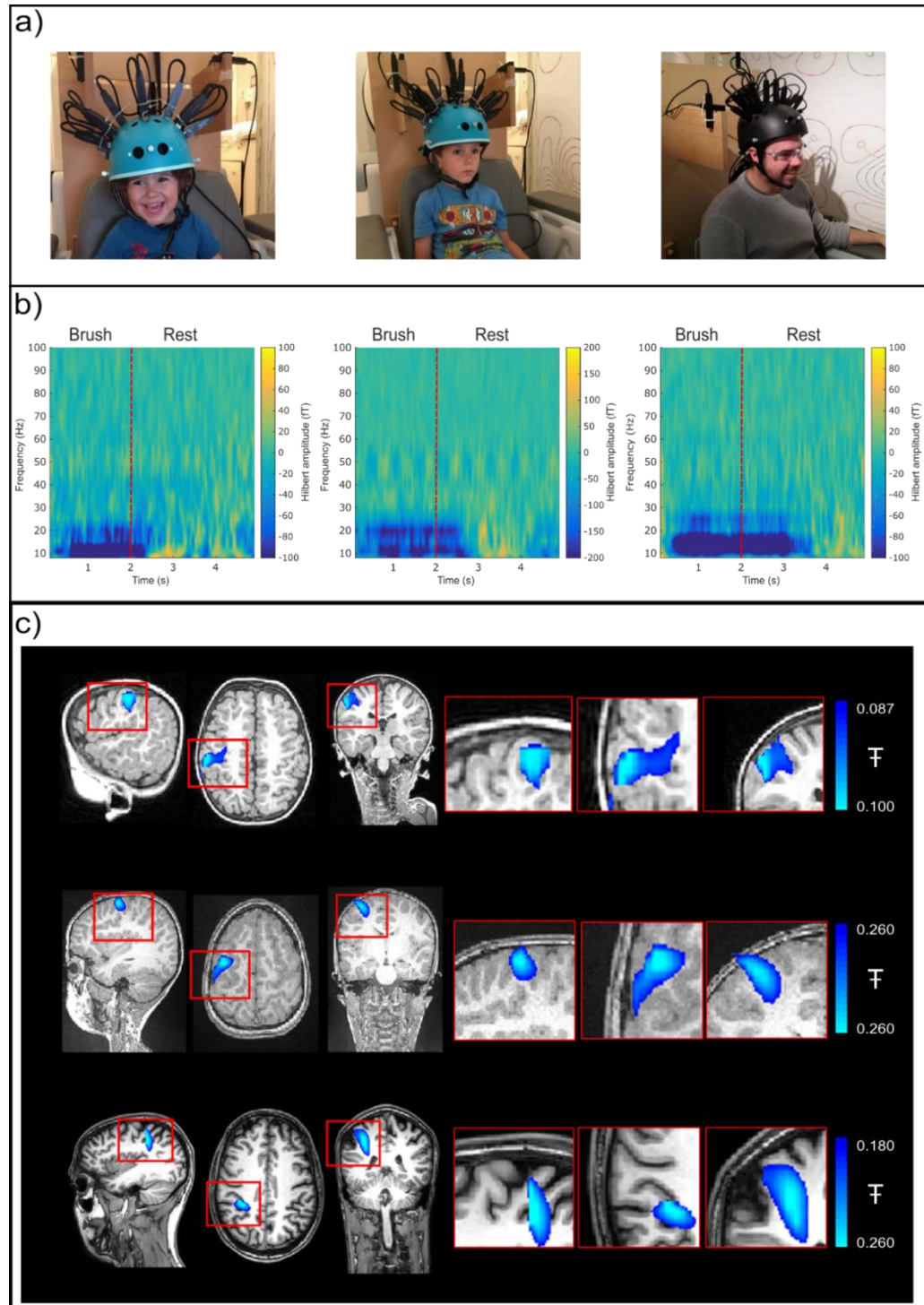


Figure 5.5: A paediatric MEG system. a) Experimental set up for three participants age 2- (left), 5- (centre) and 24-years (right). OPMs, housed in a modified bike helmet, measured the MEG signal. b) Time-frequency spectra from a single (synthesised gradiometer) channel. Changes in neural oscillations are shown; blue indicates a reduction in oscillatory amplitude relative to baseline; yellow indicates an increase. Note reduction in beta (13-30Hz) and mu (8-13Hz) amplitude. c) The spatial signature of beta modulation during the period of tactile stimulation ($0 < t < 2$ s) (blue overlay). Top: 2-year-old. Middle: 5-year-old. Bottom: 24-year-old. Note that the anatomical MRIs for the children (Top and Middle) are pseudo-MRIs chosen by the closest fit to their head shape from a database.

5.3.2 Robin Hood

Figure 5.6a shows recorded finger trace for each of the three crosshair speeds (the speed at which the crosshair moved across the screen, with faster movements being more difficult to hit the targets). The coloured lines are a single example trace from a single trial, and the average and standard deviation across all trials of that speed shown by the shaded regions. The sensor-level MEG results are shown in Figure 5.6b. In the upper plot, the line thickness indicates which gradiometer pairings showed the largest beta band response. The beta response itself is shown below in the time-frequency spectrogram, with the expected desynchronization during movement shown clearly (Heinrichs-Graham, 2016; Jurkiewicz, 2006; Pfurtscheller and Lopes da Silva, 1999).

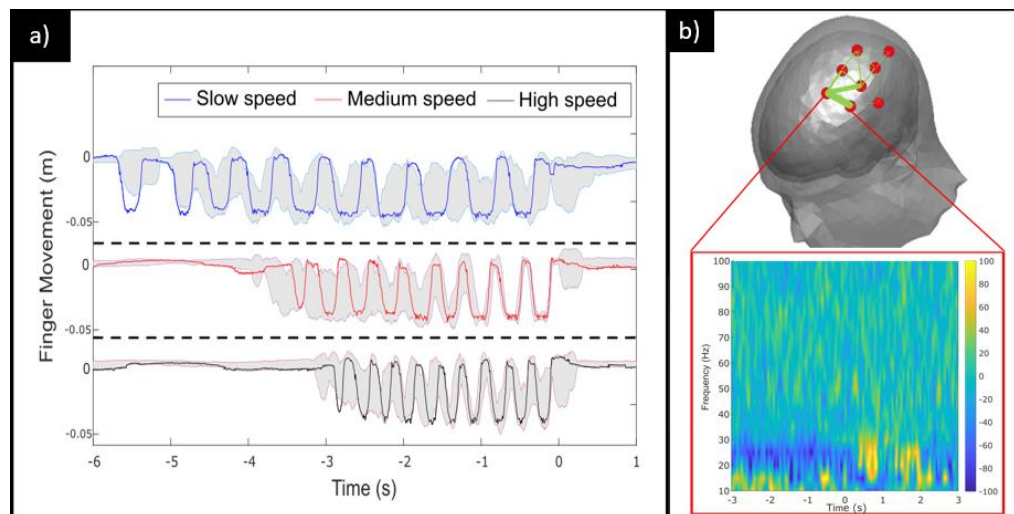


Figure 5.6: An interactive motor paradigm. a) Measured finger movements for three different speeds of cross hair movement. The shaded area shows the average and standard deviation across trials whilst the solid line shows a single example trial. b) Beta responses in a single 14-year-old participant. The upper plot shows a schematic diagram of the positions of the OPMs; the thickness of the line denotes the strength of the change in beta amplitude for all gradiometers. The lower plot shows a time frequency spectrogram from the most anterior gradiometer pair, with time zero representing the offset of movement, measured from the recorded finger movement; all trials have been averaged.

5.3.3 Ukulele

A summary of the ukulele experiment is shown in Figure 5.7. In Figure 5.7a, the experimental setup is shown, with the on screen display at the top

and the experimental setup below. Figure 5.7b shows measured head and right hand movement, as well as the recorded sound made by the instrument. A single example trial is shown (in which the participant only managed to play three of the five chords). In this naturalistic motor learning task, the participant had to make natural head movements, as they looked first at the chord pattern on the screen, and then at the frets on the ukulele to form the chord. These head movements were measured to be 4.73 ± 1.21 cm (translation) and $28.1^\circ \pm 6.71^\circ$ (rotation) (average $\pm$ standard deviation in the dominant direction across trials). Despite the substantial head movement that was required to complete the task, clear electrophysiological responses are observed in the time frequency spectrum shown in Figure 5.7c, including both the expected beta (Pfurtscheller and Lopes da Silva, 1999) as well as gamma band responses (Gaetz et al., 2013).

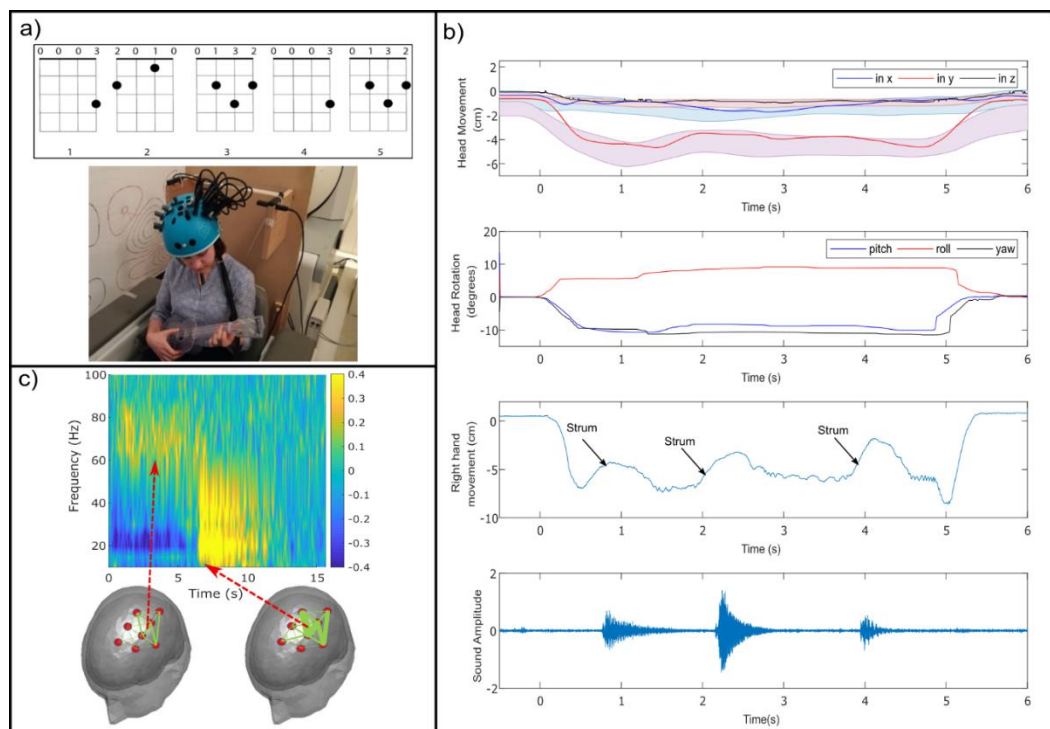


Figure 5.4: Naturalistic motor learning. a) Experimental set up with a participant playing a musical instrument. Inset image shows what the participant saw on the screen. b) Measured head and right hand movement showing the timing of when the ukulele was strummed. The lower trace shows the sound generated. c) Schematic diagram of sensor placement; the line thickness denotes the strength of the effect in the gamma band (left) and the beta band (right). Time frequency spectrum shows the neural oscillatory response from the gradiometer pair indicated by the dotted red line.

5.4 Discussion

This chapter has described the practical demonstration of a generic, lifespan-compliant, motion robust, OPM-MEG system. The simulations presented in Chapter 4 demonstrated that a simple, modified bicycle helmet offered a good compromise between high signal strength (getting sensors as close as possible to the head), and a practical and ergonomic design that could be deployed across all ages, and would be well tolerated by children. Using the techniques described in Chapter 4, we developed a system to provide a snapshot of how a single OPM-MEG device (with differently sized helmets) could be deployed to better understand neurodevelopment in young children (aged 2- and 5-years), during adolescence (a 14-year-old), and in adults. Importantly these data show the feasibility of the technique to generate high quality data, even in a two year-old child (typically the hardest age to scan without sedation). Further we have shown that OPM-MEG enables us to measure brain activity during naturalistic motor paradigms.

Our movement controlled computer game represents a paradigm with significant potential for future use in understanding development of motor skills. Our game was simple – move a finger to fire an arrow – nevertheless it is easy to conceive more complex scenarios to test motor coordination (games along the lines of those developed for Microsoft X-box Kinect or Nintendo Wii might be possible). Further, motion tracking generates important and accurate data on how and when participant movement occurs. These data are particularly important in neurodevelopmental paradigms where infants and young children are less likely to follow instructions. Here, we only had a single tracking camera and this limited the number of markers that we were able to track simultaneously. However, there is no reason why an array of tracking cameras could not be used to measure a host of additional data; examples could range from measurements of posture and head position in babies (known to be important to characterise attention and engagement) (Leong and Schilbach, 2019) to whole hand morphology to measure dexterity in older

children. This kind of tracking would enable capture of the critical timing and motion parameters necessary to carry out neuroimaging analyses in naturalistic experiments – e.g. measuring when a child plays with a toy, and which fingers they are moving.

The idea of naturalistic stimulation was taken a step further (here in an adult) via a paradigm where a person who had no previous experience of playing a stringed instrument learnt to play a ukulele. Successfully recording the electrophysiological data required that the technology could cope with a range of motions including: (i) rotating the head back and forth to look at the visual representation of the chords and the frets; (ii) moving the left hand to form the chords; and (iii) moving the right hand to strum the strings. Despite head (and hence sensor) translations and rotations >7 cm and $>30^\circ$, we were able to capture expected electrophysiological responses in both the beta and gamma frequency bands. This demonstration highlights the possibility to implement a naturalistic motor experiment in which the neural substrates underlying motor learning are probed.

There are some limitations to the current study. Most importantly, we used a limited number of OPMs which meant only a fraction of the head was covered. Clearly a complete system would require whole head coverage (similar to that simulated in Chapter 4 with e.g. 81 sensors). There is no fundamental reason why the current system cannot be expanded by adding more OPMs. The only theoretical concern is cross-talk between sensors, however this is a minor consideration since at the current sensor spacing cross-talk generates only $\sim 3\%$ error in sensor gain (Boto et al., 2018), which can be easily accounted for in source modelling. By not modelling crosstalk effects, there is a discrepancy between the data and the lead fields which would lead to an incorrect source reconstruction. For this demonstration, we deemed this small change acceptable and did not account for it in our source model, particularly when it is already restricted by the low sensor count. A more

practical issue is system weight. Each OPM weighs 20 g and so an 81 channel system, including the helmet, would weigh ~1,800 g. Further, the cables to each OPM currently weigh 33 g/m, and cables hanging from the head cause torque which could become uncomfortable for long experimental durations, particularly for younger participants. However, these problems are solved by the availability of a new generation of commercial OPMs (Boto et al., 2019) which are smaller ($1.24 \times 1.66 \times 2.44 \text{ cm}^3$), lighter (4 g), and use lighter cabling (3.3 g/m). This means that the weight of an 81 channel system could be as low as 500 g, with cable weight being negligible. The remaining chapters of this thesis present work using these new sensors, and the new solutions needed to create an OPM-MEG system with whole-head coverage.

This study is also limited by the low number of participants included in each study paradigm. However, the neurophysiological effects that we demonstrate have previously been robustly observed in larger subject groups, in both adults (Pfurtscheller and Lopes da Silva, 1999) and children (Liao et al., 2015). Our aim was to show proof of principle that these well documented responses could be seen clearly using OPM-MEG in individual participants. We have concentrated our findings on beta band effects at the expense of other important neuromagnetic signals (though we also see mu and gamma band effects). However, effects in other bands (e.g. theta) and evoked responses (Boto et al., 2017) have been shown in previous work and so there is no reason to suspect that similar responses would not be seen using the present system design. Finally, limited scalp coverage and low sensor count means that source localisation is intrinsically constrained to specific brain areas (i.e. we will only localise sources under the sensors). Nevertheless we have shown the expected left hemisphere lateralisation of sensory and motor responses.

Another limitation in this work is the MSR. Originally designed to house the CTF cryogenic system, it had an offset field of ~30 nT, whereas OPM-optimised rooms have fields of ~1.5 nT. Whilst the coils inside this MSR reduce

the field, in an OPM room the coils can operate in a different regime (for example, sensors can be moved around the room without exceeding their dynamic range to map the field rather than remaining static behind the participant) and potentially provide offset fields of ~ 0.1 nT. This would greatly reduce the effect of head movement during scanning and allow for lower frequency fields from the brain to be detected. The CTF system itself also obstructs the OPM setup such that any equipment has to be built around it, rather than being built in the best and most convenient way possible. The remaining chapters in this thesis use an OPM-optimised room to perform OPM-MEG experiments.

In summary our OPM-MEG system, with generic helmet design, paves the way for a new approach to neurodevelopmental research. We have designed a system with complete lifespan compliance that gives the opportunity for participants of all ages to take part in a range of tasks without the need to restrict participant movements. Moving forward, we need to expand our system to provide whole-head coverage so that we can scan multiple brain regions simultaneously. To do this, we must design a new helmet, similar to the bike helmet in principle, which can securely house the new generation of OPM sensors.

Chapter 6: Designing a whole-head OPM system

In this chapter, we design a whole-head OPM-MEG system using Gen-2 OPMs. We first show that it is not feasible to use a bike helmet as in the previous chapters as the sensors cannot be kept cool enough, and by having slots all around the head, the helmet loses its integrity. Nevertheless, the principle is still viable and we therefore present two methods of holding sensors on the participant's head: a rigid, additively manufactured helmet that uses the same principles as the bike helmet, and a flexible EEG-style cap. We develop a co-registration procedure for each design, and show how the co-registration errors manifest differently for each design (with the rigid helmet having a systematic error and the flexible cap a random error). We then assess how these errors affect source reconstruction in simulation, and show that the rigid helmet performs better. The rigid helmet is also shown to have better whole-head coverage as sensors can be placed over the ears and jaw, but this comes at the cost of signal amplitude as the sensors are set back from the head to accommodate multiple head shapes. The flexible cap is able to place sensors almost directly on the scalp as it can more easily adapt to the participant's head shape. Finally, we address some of the issues of creating a larger system array, namely solving cable management issues and reducing the crosstalk between cables as they move over one another during scanning. The methods and results presented in this chapter have been published in Hill et al., *Neuroimage* (Hill et al., 2020).

6.1 Introduction

In the previous chapters, we have shown that an OPM array can, in principle, be adapted to any head size. In addition, when background fields are controlled (Holmes et al., 2018; Holmes et al., 2019) it is feasible to collect data whilst a participant moves (Boto et al., 2018; Hill et al., 2019). By using a modified bike helmet to house the sensors, we designed a system with complete lifespan compliance that gives the opportunity for participants of all ages to take part in a range of tasks without the need to restrict their movements.

Although the experimental results in the previous chapters offer exciting potential, significant development is still required. Whilst multi-channel systems are available (Borna et al., 2017; Boto et al., 2018; Iivanainen et al., 2019b), most demonstrations (including the work in Chapters 4 and 5) still employ small numbers of sensors sited over specific brain regions and the introduction of a whole-head array will be an important step forward. Sensor array coverage (i.e. where to place OPMs to cover all possible cortical locations) and the number of OPMs required to gain parity of performance with cryogenic systems remain open questions (Iivanainen et al., 2019a; Tierney et al., 2019b) and there are, to date, few studies comparing OPM and SQUID measurements (Borna, 2020; Boto et al., 2017; Iivanainen et al., 2019c). Such comparisons are vital if the MEG community is to gain confidence and adopt OPM technology.

Critical to the ultimate design of a viable OPM-based MEG system is the way in which OPM sensors are mounted on the head. This design must represent a balance of four critical considerations: first, sensors must be sited close to the head to pick up maximum signal, and rigidly held in position (i.e. no movement relative to the head) to avoid artefacts. Second, we need accurate knowledge of the sensor locations and orientations relative to each other, and relative to brain anatomy – this is imperative for data modelling. Third, the helmet must be ergonomic and practical (for both participant and

operator). Finally, since the current commercially-available sensors require heating of the Rb-87 vapour cell in order to operate in the spin exchange relaxation-free (SERF) regime, the helmet design should allow heat to escape from the OPM and its mounting. In the previous chapter, the bike helmet idea facilitated a number of these properties: 1) the sensors were rigidly held in place; 2) their locations were accurately known; 3) the helmet was ergonomic and practical. However, it only worked with limited coverage, and it's not clear whether this idea would scale to a whole head system.

In this chapter, we begin by showing that the bike helmet idea is, in fact, impractical. However, we move on to design a 'whole-head' (49-channel) wearable OPM-MEG system using commercially-available sensors (QuSpin Inc.). We contrast two different OPM helmet designs: a flexible (EEG style) cap, and an additively-manufactured, generic, rigid sensor-cast. We contrast the trade-offs between flexibility (which ensures OPMs are close to the scalp) and rigidity (which enables accurate knowledge of sensor locations for source reconstruction) in simulation, and we introduce and evaluate new optical techniques for co-registration of sensor locations to brain anatomy for both helmets.

6.2 Bike helmet 2.0

As shown in Chapters 4 and 5, a very low cost, ergonomic and lightweight bike helmet can be modified to hold Gen-1 QuSpin OPM sensors over specific regions of the brain. We also developed a co-registration procedure using a combination of a CT scan of the helmet and a motion tracking camera, which allowed us to successfully source localise brain activity across several participants of varying ages. However, the weight of the Gen-1 sensors (each sensor weighs 20 g) and their cabling (weighing 33 g/m) would make it difficult to achieve whole head coverage using the same approach. Fortunately, a new generation of OPMs were manufactured which are considerably smaller ($1.24 \times 1.66 \times 2.44 \text{ cm}^3$), lighter (4 g per sensor), and use lighter cabling (3.3

g/m) (see Figure 6.1). This meant that more sensors could be placed inside a bike helmet without adding as much weight, and the lighter cabling would mean less torque on the head despite having a much larger sensor array.



Figure 6.1: Gen-1 vs. Gen-2. Comparison of the two generations of QuSpin OPM sensors with a coin for reference. Adapted from Osborne et al. (Osborne et al., 2018).

We initially tried to redevelop the bike helmet for Gen-2 OPM mounting. In order to hold the sensors in the helmet, holes were cut in a similar fashion to the previous Gen-1 design (Figure 6.2A). However, because the Gen-2 sensors are smaller, they could not simply be held in place by the polystyrene in the helmet. Instead, we manufactured ‘holders’ which would slot into the helmet with the sensors placed inside them (Figure 6.2B). Each holder has a stem that can be secured to the outside of the helmet to hold them rigidly during recording. A 3D digitisation of the helmet was achieved again using a volumetric CT scan (identical to the one described in Chapter 4) with all holders in place (Figure 6.2C).

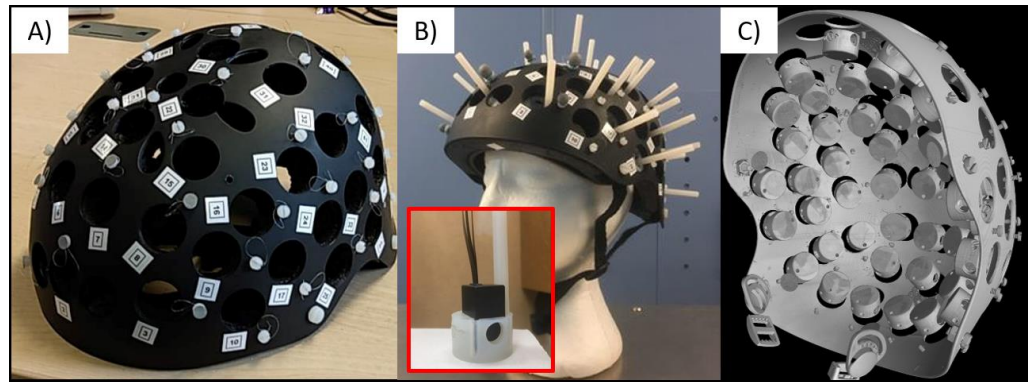


Figure 6.2: Bike Helmet 2.0. A) An adult bike helmet with slots cut to hold Gen-2 OPMs. B) The helmet with sensor holders in place. The sensor is placed into a holder (shown inset) and secured to the helmet by the stems that can be seen sticking out of the helmet. C) Volumetric CT scan of the helmet with the holders in place in order to determine sensor locations and orientations.

The bike helmet in the previous chapters showed us that a generic design is feasible and that an ergonomic helmet design is the best solution for scanning a range of participants (especially children). While this design could work in principle, there were several practical issues we encountered when adapting the helmet for whole-head coverage that prevented us from using it. First, we found that, after several minutes use, the sensors would overheat and turn off to prevent them from being damaged. Indeed, we have shown that it was possible to control the temperature of the Gen-1 OPMs in the bike helmet in Chapter 4 using pyrolytic graphite, but the Gen-1 sensors had a much larger surface area in contact with open air. This allowed them to disperse the heat out of the helmet, with the pyrolytic graphite aiding dispersion. Because the Gen-2 sensors are much more compact they are completely covered by the polystyrene, preventing any contact with open air. Second, the increased amount of holes made in the helmet reduced its structural integrity. This means that the sensor holders could be in slightly different positions each time they are removed and re-inserted, and gradual wear and tear would reduce the rigidity further, thus eliminating one of the most desirable features of a rigid helmet – the accurate knowledge of sensor locations. Finally, the helmet did not cover the entire occipital lobe nor any of the temporal lobes (though this could ostensibly be solved using a different bike helmet).

For these reasons, we embarked on a collaborative project with Added Scientific Limited (ASL) to design a rigid helmet that had all of the attributes of the bike helmet but could provide the features we need such as: full coverage of the head; contact with open air to aid temperature management; and a purpose built structure to hold the sensors rigidly in place. In doing so, we have also embarked on one of the first steps towards commercialisation of our OPM-MEG system.

6.3 Helmet design

We employed two contrasting solutions to address the needs for our whole-head system:

Flexible cap: This is based on an ‘EEG-style’ cap. It contains 63 sensor mounts (see Figure 6.3A) and is manufactured by QuSpin. The cap is made from elasticated fabric, which is given structure via incorporation of boning. The boning comprises a number of rigid plastic wires which are sewn into the cap to help maintain its shape, and to limit OPM movement relative to the scalp. Whilst this gives some structure, the cap remains easily stretched and so readily adapts to any (adult) head shape (it would be easy to manufacture this cap in several sizes to accommodate other age groups). The sensor mounts were 3D printed to house QuSpin Gen-2 sensors, and made from plastic. They hold the sensors at the corners without enclosing them and so heat is able to escape from the external sensor surfaces through natural convection. The sensor layout is based on the 10-10 EEG system. Flexibility of the cap ensures that sensors are reasonably well positioned close to the scalp surface and so measure high signal (with the caveat that, for individuals with long hair, their hair can push the sensors off the scalp). The cap is also light-weight and comfortable to wear for the participant, with a total weight of 309 g (when containing 49 Gen-2 sensors). However, the flexibility also means that neither the locations nor orientations of the sensors, both relative to one another and relative to the brain anatomy, are known a-priori and this information must be found using a co-registration procedure.

Rigid helmet: In addition, working in collaboration with ASL, we designed and built an additively manufactured rigid helmet (Figure 6.3B) from PA12 (which is a nylon polymer) using an EOS P100 Formiga Laser Sintering machine. The size and shape of the inner surface of the helmet is based on a set of adult MRIs; the scalp surfaces were extracted from 9 MRI scans (co-registered together beforehand) and these surfaces were superimposed, to produce a composite head shape (Figure 6.3C). This surface was grown radially by 1.5 mm to form a helmet inner surface that will accommodate the majority of adults' heads. Ear pockets were incorporated into the design to improve its wearability and comfort. Understandably, the resulting shape is a "one-size-fits-all" solution due to the helmet's rigidity (i.e. it cannot adapt to head shape); for any single individual there is naturally an inhomogeneous gap between the scalp surface and the sensors. This gap was found to range in size over the scalp surface from 1.9 mm to 26.0 mm (median 7.2 mm) for a representative adult male. Whilst any gap is non-ideal, this was significantly smaller than that for a cryogenic MEG system (13.1 mm to 38.8 mm for the same participant (median 26.7 mm)). In the future it would be possible to build this helmet in multiple sizes to better accommodate variation across a normal range of head sizes.

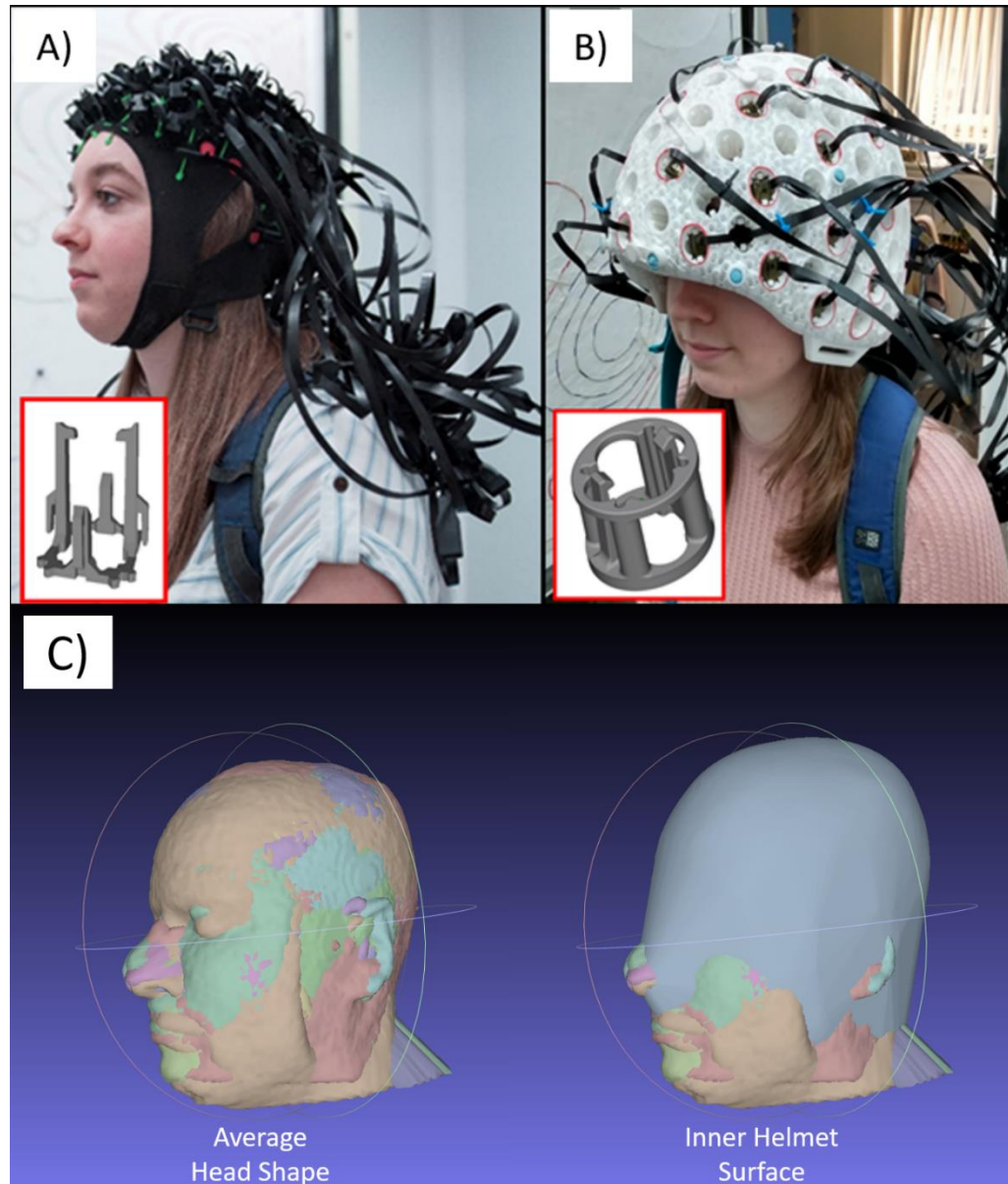


Figure 6.3: Two whole-head system designs. A) Flexible cap based on an EEG cap. The sensors are held to the cap using clips shown in the insert. B) Rigid additively manufactured helmet. The sensors are slotted into push-fit holders inside the helmet shown inset. C) 9 anatomical MRI scans co-registered together, and superimposed. The average head shape was found and grown radially by 1.5 mm to encompass the majority of adult head shapes.

The rigid helmet contains 133 cylindrical mounts, each of which can hold an OPM sensor rigidly at its corners, eliminating the motion of any one sensor relative to all other sensors. The cylindrical design left space around each of the sensors which was opened up to increase air circulation, enabling the natural convection of heat away from the sensors and also from the participant's head. This contrasts the bike helmet setup, where all sensors were covered by the polystyrene, preventing any air flow within the helmet. The

space between the sensor mounts was filled with a matrix-based gyroid triply periodic minimal surface lattice. This provides a lightweight and mechanically-rigid structure, while also facilitating the natural convection of heat away from the head, allowing the participant to feel more comfortable by enabling the flow of air to the scalp

A critical feature is that, although the sensors are not necessarily positioned as close as possible to the scalp surface, the relative locations and orientations of the sensor mounts are known to a high level of accuracy. This is because a complete digital representation of the helmet exists, and the tolerance of the 3D printing process is approximately 300 μm . This means that the sensor casing can be located extremely accurately. Further, the tolerance to which the OPMs are built is approximately 200 μm (QuSpin Inc.). This means that the location of the sensitive region of the cell, and the orientation of the on board sensor coils (which ostensibly determines orientation sensitivity of the sensor) relative to the rest of the helmet is likely known to within an accuracy of less than 1 mm and 1 degree.

6.4 Co-registration

As discussed in Chapter 4, one of the main issues when using generic systems for mounting sensors on the head is co-registration. The rigid helmet can use a similar procedure to the bike helmet in Chapters 4 and 5 as the sensor positions are known a-priori and are fixed in place relative to each other (i.e. the 3D design used for printing the helmet replaces the X-Ray CT data). This means we only need to find the position of the helmet relative to the head in order to gain knowledge of all sensor positions and orientations. However, the flexible cap allows the sensors to move relative to each other on the participant's head, so their relative positions cannot be known a-priori. Here, we develop a new co-registration procedure for each design.

A 3-dimensional optical imaging system (Structure IO camera (Occipital Inc., San Francisco, CA, USA) coupled to an Apple iPad, operating with Skanect software) and an anatomical MRI scan, were used for co-registration of OPM sensor locations to brain anatomy (Homölle and Oostenveld, 2019; Zetter et al., 2019). The whole-head MRI scan was generated using a 3 T Philips Ingenia system, running an MPRAGE sequence, at an isotropic spatial resolution of 1 mm. The co-registration procedure, for the two helmet types, was as follows:

Flexible cap: OPMs were removed from the sensor holders and coloured markers were added in their place (one per sensor). The structure camera was used to acquire a 3-dimensional digitised surface representing the participant's scalp and face, along with the markers. A colour-thresholding technique was then used to extract the markers, and in this way the locations where the OPM casing met the cap (hence scalp) were derived. OPM orientation was taken to be perpendicular to the scalp surface, at the location of the sensor. A surface matching algorithm fitted the scalp and face surface from the optical scan to the equivalent surface extracted from the anatomical MRI scan, thus resulting in complete co-registration of the surface sensor locations/orientations to brain anatomy. The sensitive volume of the OPM (the cell) is located 6.5 mm radially inwards from the outer casing, and is shifted 2 mm tangentially (i.e. the OPM is asymmetric). We therefore approximated the location of the cell as being 6.5 mm radially from the location of the surface marker. Unfortunately, it was not possible to account for the asymmetry as the rotational position of the sensor on the cap is unknown. This procedure is summarised in Figure 6.4A. Note that it was not possible to add the coloured markers to the OPMs directly while they were placed in the cap, as the surface to be mapped by the structure camera then became too convoluted. It is for this reason that removal of all OPMs prior to digitisation is necessary. Unfortunately this adds significantly to overall set up time.

Rigid helmet: The relative locations and orientations of the sensor casings are known a-priori and this simplifies the procedure, such that it is sufficient to generate a mapping between the helmet and the head (rather than between each sensor and the head). Co-registration was done in two stages. First, 6 coloured markers were placed at known locations on the helmet, and a further 4 were placed on the participant's face. The camera and colour-thresholding were then used to map the relative locations of these markers, allowing mapping of the helmet to the face. Following this, the helmet was removed and the participant was asked to wear a swimming cap (to flatten down their hair). A second digitisation was acquired of the markers on the face, relative to the rest of the head surface. The head surface was then fitted to the equivalent surface extracted from the anatomical MRI scan. Combining two transforms (helmet-to-head and head-to-MRI) we were able to effect a complete co-registration of sensor casing to brain anatomy. In order to approximate the location of the cell, the 6.5-mm radial offset was added, and because the rotational position of the OPM was known, the 2-mm tangential offset was also added (accounting for the asymmetry in the helmet). This procedure is summarised in Figure 6.4B.

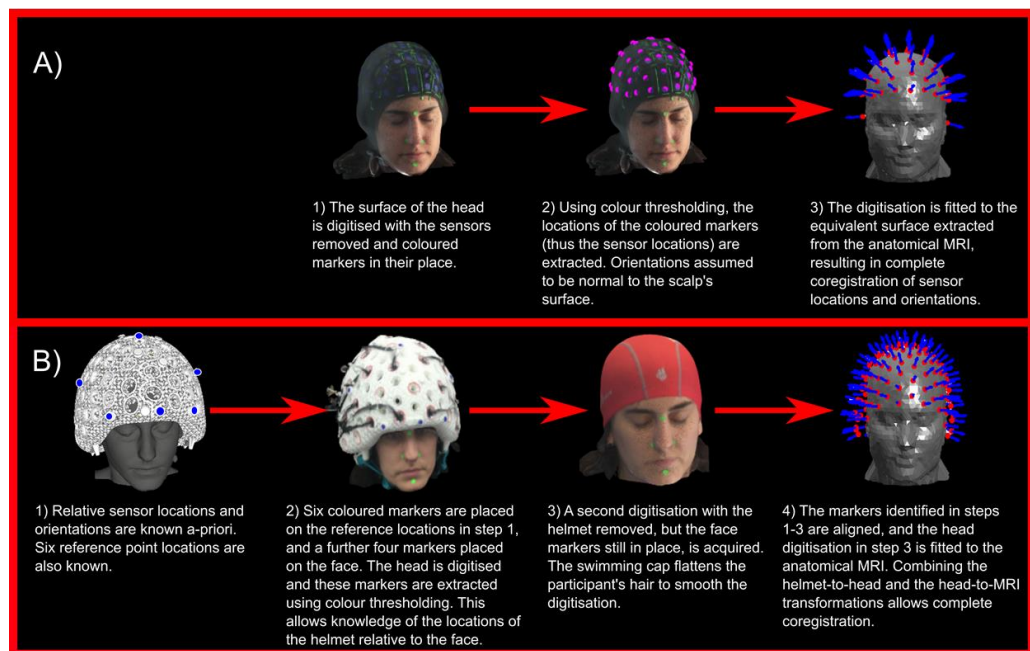


Figure 6.4: Schematic diagram showing co-registration algorithm. A) Flexible cap. B) Rigid helmet.

6.4.1 Co-registration accuracy

To estimate the accuracy of co-registration, we sequentially placed the two helmets on a single participant, and ran each of our co-registration procedures 10 times. Care was taken to ensure that the helmets did not move between acquisitions. For every sensor, we measured its mean location/orientation (across runs). We then measured the average Euclidean distance from the mean location (across runs) as an estimate of random error in location. Similarly, the average angular difference from the mean orientation was taken as orientation error.

Figure 6.5 shows the accuracy of our co-registration procedures for both helmet designs. The error was calculated for each sensor separately [note that these values only provide an estimate of *random* error; i.e. if there was a *systematic* error affecting each run in the same way, it would not be reflected here. However, such an estimate of systematic error would be impossible without a ground truth sensor location/orientation]. In the figure, the upper panels show the results from the rigid helmet and the lower plots show those from the flexible cap; the left-hand plots show error in sensor position whilst the right-hand plots show error in orientation. Quantitatively, results show that for the rigid helmet, the average location and orientation errors (across sensors) were 3.9 mm and 0.94° respectively. The maximum errors at any one sensor were 5 mm and 1.1° , and these tended to occur close to the back of the helmet. This is unsurprising since we used the front of the helmet and the face for co-registration, and small errors at the front of the head will cause rotational inaccuracies which will be amplified at the back of the head. For the flexible cap, the average location and orientation errors were 2.6 mm and 1° and the maximum errors were 3.6 mm / 1° . Here, again, the spatial topographies showed that the largest errors were towards the back of the head. This is likely because the surface matching depends largely on facial features. [Note, that the orientation errors for the flexible cap are based on the

normal of the scalp surface, not the true sensor orientation which we are unable to determine in the flexible cap. These errors are almost certainly larger than shown here].

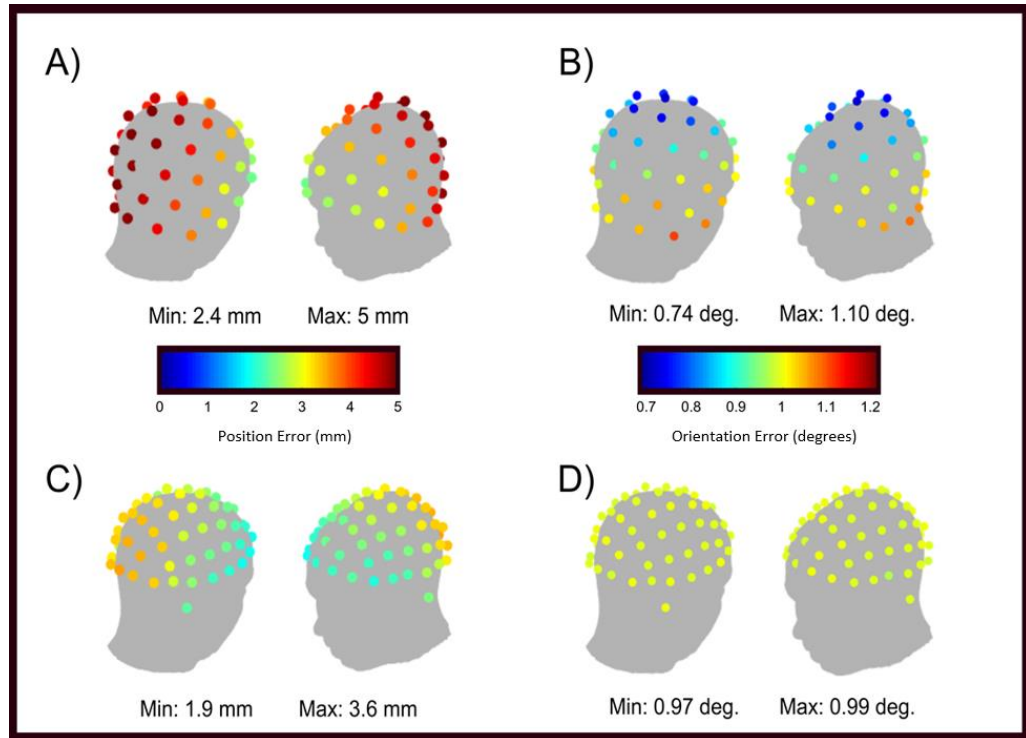


Figure 6.5: Test-re-test co-registration errors. A) Location error for rigid helmet. B) Orientation error for rigid helmet. C) Location error for flexible helmet. D) Orientation error for flexible cap. Colder colours indicate a more reliable co-registration at that sensor.

Importantly, the magnitudes of these errors are relatively small and approximately in line with the co-registration errors typically reported for cryogenic MEG (Adjamian et al., 2004; Chella et al., 2019; Hillebrand and Barnes, 2011; Whalen et al., 2007). For the rigid helmet, these error values reflect how accurately we know the location of the helmet relative to the brain (since the sensor locations, relative to each other, are known accurately from the additive manufacturing procedure). Conversely, for the flexible cap, errors reflect how accurately we know sensor positions relative to the brain, and relative to all other sensors.

It is perhaps surprising that, overall, the uncertainty is larger for the rigid helmet, however we believe that there are two reasons for this: first, the

co-registration for the rigid helmet is a two-step process (see Figure 6.3B). This means that there are potentially two sources of error. Second, the mapping is reliant on a relatively small number of markers – 6 on the helmet and 4 on the face – meaning that if just one of the markers is in the wrong place, the co-registration procedure will have increased error. Also, these markers are located at the front of the head which likely explains why error is minimised at the front and larger at the back. In future, it is likely that the accuracy of co-registration for both helmet designs could be improved – for example by the use of more markers on the face and more markers on the rigid helmet.

6.5 Effect of co-registration error in simulation

A key point from section 6.4 is that the co-registration error manifests differently in the two cases. For the rigid helmet, any error in co-registration affects all sensors in a similar way (i.e. co-registration error is ‘systematic’) since the relative sensor locations are known very accurately (from the 3D printing process). Conversely, for the flexible cap, we require separate co-registration of each sensor location and orientation. Co-registration error is therefore different for each sensor and consequently manifests as a ‘random’ error.

In order to investigate how source localisation behaves in the presence of such co-registration errors, simulations were undertaken. A single tangential dipolar source was simulated inside a spherical volume conductor (8-cm radius), at a depth of between 2 cm and 2.4 cm from the sphere surface (to approximate a cortical dipole) but otherwise location was randomised. We simulated 49 magnetometers placed 6 mm above the sphere surface and approximately equidistant from each other, covering the upper half of the sphere. The source time course comprised Gaussian random data with standard deviation 1 nAm and this was projected through a forward solution based on a single sphere head model and the dipole equation derived by Sarvas (Sarvas, 1987). Uncorrelated Gaussian noise was added to each simulated sensor time course with an amplitude of 50 fT (an approximate SNR of 1, at the

most affected sensor, depending on source depth). A total of 300 s of data were simulated at a sampling frequency of 600 Hz.

We incorporated co-registration errors by both translating the sensor location, and rotating the sensor position and orientation about the origin (which was set as the centre of the sphere). These errors were applied in two ways:

- 1) **Flexible cap:** To simulate co-registration error using the flexible cap, the error was applied independently to each sensor. The magnitude of the error (e.g. a 1-mm translation and 1-degree rotation) was the same for all sensors, but the direction of these errors were random to simulate the effect of having to determine each sensor location separately via a co-registration procedure.
- 2) **Rigid helmet:** To simulate the rigid helmet, the same co-registration error was applied to all of the sensors, mimicking the case where the relative locations of the sensors are known accurately, but the error manifests as a shift of the entire helmet on the participant's head.

Note that the magnitudes of the errors are the same in both cases; the difference between the two helmet designs is simply in terms of how the error manifests – systematic or random across sensors. We simulated 21 error magnitudes, starting at zero, up to 10 mm and 10 degrees (translation and rotation errors were both applied with equal numerical magnitude in mm and degrees, respectively). Examples are shown in Figure 6.6A. For each error magnitude the simulation was run for 30 iterations, with new (randomised) dipole location each time

Data were reconstructed using a beamformer. Data covariance was computed in a time-frequency window spanning all 300 s and the 1-300 Hz frequency range. In order to investigate the effect of regularisation, we regularised the covariance matrix using the Tikhonov method, with a regularisation parameter equal to either 0, 0.1, or 0.4 times the maximum

singular value of the unregularised matrix (i.e. no regularisation, 10% or 40% regularisation). We computed three summary measures to estimate the beamformer effectiveness:

- **Localisation accuracy:** An image of beamformer-projected source power, normalised by noise (i.e. the pseudo-Z-statistic (Vrba and Robinson, 2001)) was generated within a 12-mm cube, centred on the original simulated source location. The cube was divided into voxels (of isotropic dimension 1 mm) and for each voxel the source orientation was estimated using the direction of maximum signal to noise ratio. We determined the peak location in this image and computed the displacement between this and the true source location, as a measure of localisation error.
- **Projected power-to-noise ratio:** This was simply the pseudo-Z-statistic at the peak location in the image. Larger values typically mean a better source estimate (i.e. higher signal to noise ratio).
- **Time course correlation:** At the location of the peak in the beamformer image we calculated the beamformer-projected source time course and measured correlation between this and the simulated (ground truth) time course.

6.5.1 Results

Results are shown in Figure 6.6B. The left, centre and right panels show the correlation between simulated and reconstructed time courses, pseudo-z-statistic, and localisation error in the beamformer image, respectively. In all cases red shows results from the rigid helmet and blue shows the flexible helmet data. Solid, dashed and dotted lines show zero, 10%, and 40% regularisation, respectively. It is clear from the left and centre panels that increased co-registration error causes a decrease in both the projected pseudo-z-statistic and the correlation between simulated and reconstructed time courses. However this reduction, whilst apparent for both simulated helmet

types, is more pronounced in the flexible cap compared to the rigid cap (i.e. for the same magnitude of error, we are much more likely to be able to accurately reconstruct the temporal morphology of a source if we use a rigid helmet compared to a flexible cap). We found that regularisation lessens this effect, with the difference between the rigid and flexible caps becoming less dramatic with high regularisation (but still clear)¹⁰. These findings are supported by those of Zetter et al. (Zetter et al., 2019) who showed (also in simulation using random error) that a 4-mm co-registration error generates approximately an 8% error in source localisation for beamforming. In contrast, the right hand panel of Figure 6.6B suggests that localisation error, which increases with co-registration error as would be expected, is marginally worse for the rigid compared to the flexible helmet. These results are likely due to the lead field perturbations brought about by the co-registration errors. Put simply, if all sensors are shifted in the same direction, the measured field is likely to look similar to a modelled field, but where that modelled field originates is in the wrong location. This means that a source timecourse can still be reconstructed, but at the wrong location. In contrast, if sensor locations are randomly perturbed, the spatial signatures of the lead fields will be disrupted, and hence any modelled field will always be a poor match for measured fields. This will make the beamformer less effective and therefore the temporal morphology of the source will be poorly reproduced. However, the beamformer image may still peak closer to the true source location because, on average, the random sensor movement will average to zero. So, in summary, our simulation suggests that the beamformer is more likely to faithfully reproduce the temporal morphology of a source for a rigid, rather than a flexible cap (albeit with slightly greater localisation error).

¹⁰ It should be noted that increased regularisation means diminished spatial accuracy.

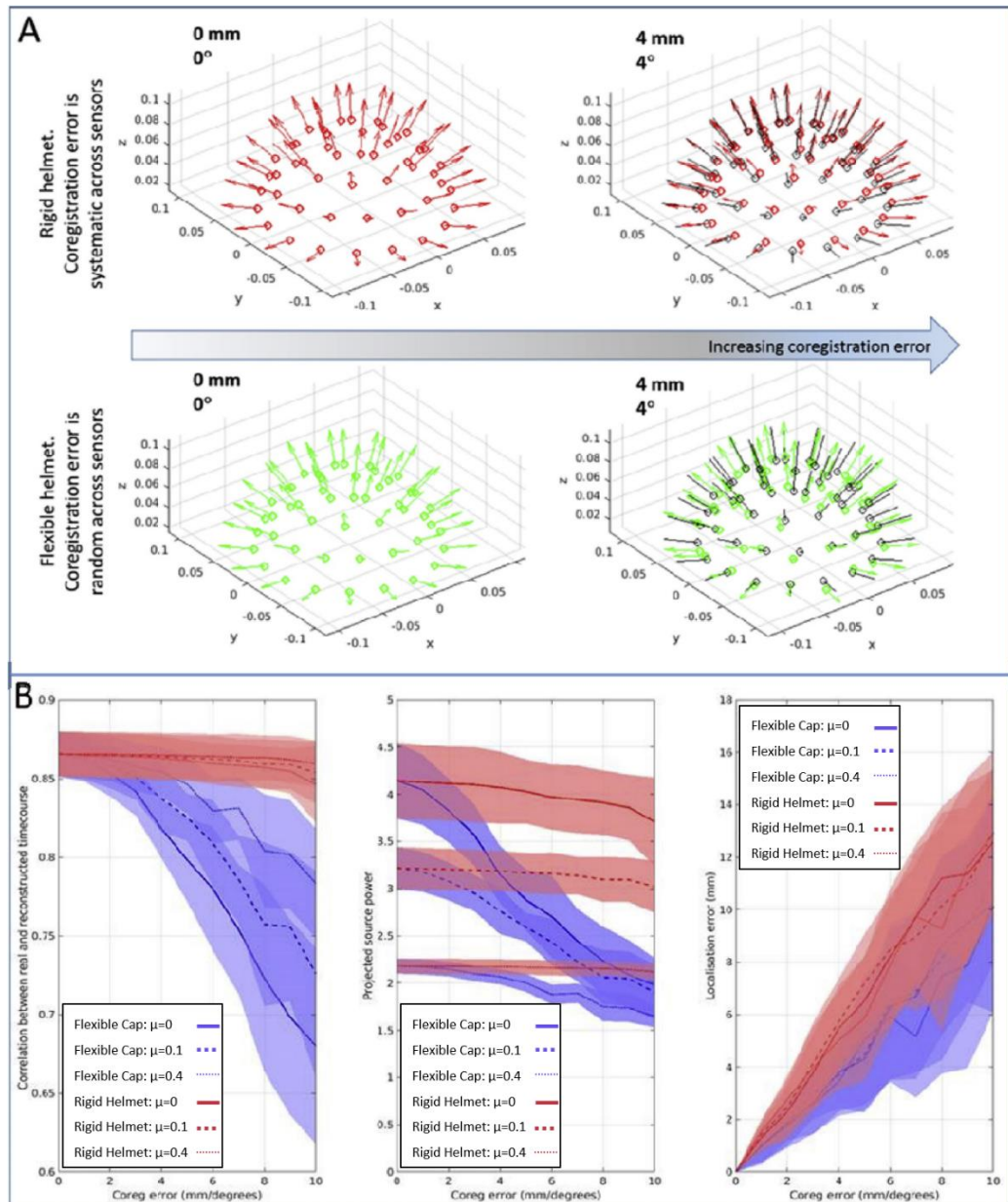


Figure 6.6: Simulation showing how beamforming is affected by co-registration error in a rigid helmet or flexible cap. A) Example of co-registration errors in the two cases. For the rigid helmet (upper panel), we assume we know the relative sensor locations and orientations accurately, so co-registration error is systematic across the helmet. For the flexible cap (lower panel), all sensor locations and orientations are acquired from the co-registration process independently, meaning co-registration error is random. The black circles show true sensor positions, and the coloured circles show measured locations with co-registration error. The left hand panel shows zero co-registration error; the right hand panel shows an error of 4 mm translation and a 4 degree rotation (about the origin). B) Summary measures of time course correlation (left) pseudo-Z-statistic (centre) and localisation accuracy (right) plotted as a function of co-registration error. Red shows the rigid cap, blue shows the flexible cap. The different lines show different regularisation values (zero (solid line); 10% (dashed line); 40% (dotted line)). Note x-axes represent both translation and rotation – e.g. an error of 5 means 5 mm and 5 degrees.

6.6 Estimating ‘whole-head’ coverage in simulation

In addition to the way in which the sensors are held on the head, the two designs also offer a different level of signal coverage. The 10-10 EEG system for the flexible cap offers 63 possible locations for the sensors to be placed, and the rigid helmet has a 133. Because we only had 49 Gen-2 sensors, the sensors had to be spread out to give the best coverage. Using the flexible cap means that much of the temporal lobe is missed by the magnetometers because it is very difficult to position sensors over the ears and the jaw in this design. This region is also an issue in a cryogenic MEG system where the temporal lobes are often outside of the array as the participant needs to see out of the helmet. Using a 3D printed helmet, it is easier to position sensors all around the head as the sensors can be held more rigidly allowing them to be placed over regions the flexible cap is unable to cover (such as the ears and the back of the jaw).

Here, we aimed to estimate the likely coverage of 3 different systems: the rigid helmet and flexible cap previously introduced, and (for comparison) a cryogenic MEG system. The cryogenic system was based on a 275-channel CTF system, but third order gradiometers were not accounted for. We divided the brain into regular 4-mm voxels, and performed a simulation similar to that described in Chapter 4.2. For each voxel, we identified the orientation of the local tangential plane (relative to the voxel location, which itself was defined relative to the origin of a sphere that best fits the participant’s head shape). We then simulated two dipoles along orthogonal orientations within that plane (i.e. we assumed that radially oriented dipoles would be magnetically ‘silent’). We calculated the forward field for each dipole using a single-sphere volume conductor model and a dipole approximation (Sarvas, 1987). For both dipoles, we determined the Frobenius norm of the forward-field patterns for each orientation; we then averaged the two values, resulting in an approximation of the total signal strength (across all sensors) from each voxel. This was repeated for all voxels, resulting in a volumetric image showing how estimated signal

strength varies across the brain, for any sensor layout. Images were formed based on 49 OPMs in the flexible and rigid helmets, and 275 channels for the conventional cryogenic system.

Figure 6.7 shows sensor positioning, and coverage in the brain for the rigid helmet (left), the flexible cap (centre), and a cryogenic system (right). In the upper plots, the red dots show the sensor locations relative to the head surface (though only one aspect is shown, coverage is approximately symmetrical). In the lower plots, the colours represent the norm of the expected magnetic field induced by a unit dipole (of strength of 1 nAm) at all voxel locations in the brain. For all three systems there is a degree of inhomogeneity across the brain with the temporal pole and cerebellum suffering the lowest sensitivity. Nevertheless, we gain reasonable sensitivity over the entire cortex, even with only 49 OPMs. Note the anisotropy of the coverage in the cryogenic system with higher signal strengths in posterior regions and lower signal strengths for the frontal lobes. This is not the case with OPMs in the rigid helmet – indicating a more even coverage. OPMs in the flexible cap also show poor coverage at the front of the head, although this is due to the physical size of the cap and its positioning on the head (to cover visual cortex)¹¹. Finally note that, as a result of sensor proximity, there is a difference in the scale of the expected fields. Both OPM systems have a marked increase in signal compared to the cryogenic system since no thermally insulating gap is required, and so sensors are positioned closer to the scalp. It's also noted that the flexible cap gets sensors closer to the scalp than the rigid helmet, hence greater signal is observed.

¹¹ It is possible that this could be corrected for in a larger cap.

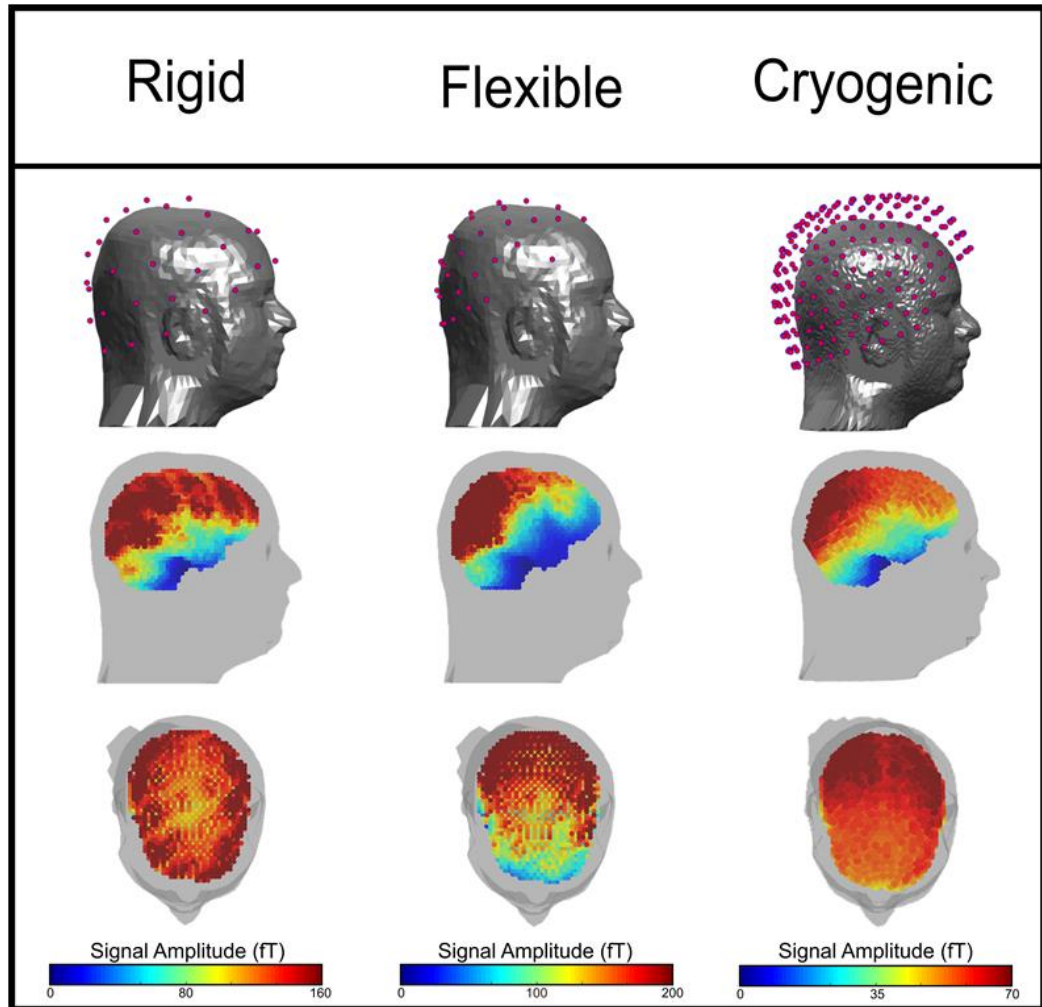


Figure 6.7: Cortical coverage. The plots on the top row show the sensor locations over the scalp. Lower plots show the norm of the forward fields, for each dipole location in the brain. Left, centre and right shows the rigid helmet, the flexible cap, and the cryogenic system, respectively. Note, the magnitude of the colour axis is different for each system.

6.7 Further considerations in a whole head system

In the previous sections of this chapter we have shown two methods which are capable of mounting Gen-2 OPMs as a wearable neuroimaging system. Simulations show that the rigid helmet offers greater coverage and more accurate source reconstruction, while the flexible cap holds the sensors closer to the scalp allowing greater signal-to-noise ratio. So while we have two potential solutions for mounting Gen-2 OPMs on the head, there are new issues that arise when using a larger array of sensors.

6.7.1 Cable management

In Chapters 4 and 5, the largest contributors to the weight of the system were the cables from the Gen-1 sensors. Because there were fewer sensors being used (24 at most) and they were only focussed on specific regions of the brain, the cables could quite easily be bundled together and supported behind the participant during the task. This reduced the torque on the participant's head and prevented the cables from obstructing the participant's view. However, because the cables are supported behind the participant, this makes it difficult to move freely; the more freedom the participant has, the more unsupported cabling is needed, and thus the more weight pulls on the participant's head.

The Gen-2 sensor design addresses the issue of cable weight by using ~60 cm of much lighter flex cable from the sensor head before connecting to the rest of the cable. This length of flex cable is long enough to allow the cable from a sensor at the front of the head to run over the top of the head and down to the participant's back, where the cables can be bundled like before. We can then use a backpack to fasten the cable bundles, allowing the participant to support the weight of the cables more easily (see Figure 6.8A). It also means that the participant can move freely without being restricted by where the cables are supported.

Because there are now so many more channels covering the whole of the head as opposed to specific regions of the brain, the cables can easily become tangled and wrapped around each other. Aside from the practical nightmare that is 50 tangled sensors, the cables also pull on each other if the participant moves which causes artefacts in the signal as the cables pull on the internal components of the sensor. In order to prevent this movement, the cables are secured to either the helmet or the cap (depending on which was used) immediately after leaving the sensor head (see Figure 6.8B). This means

that even if the cables pull on each other, the part that leads into the sensor head remains fixed in place and doesn't pull on the components of the sensor. This simple but practical solution ensures that “mechanical” cable interactions are kept to a minimum.

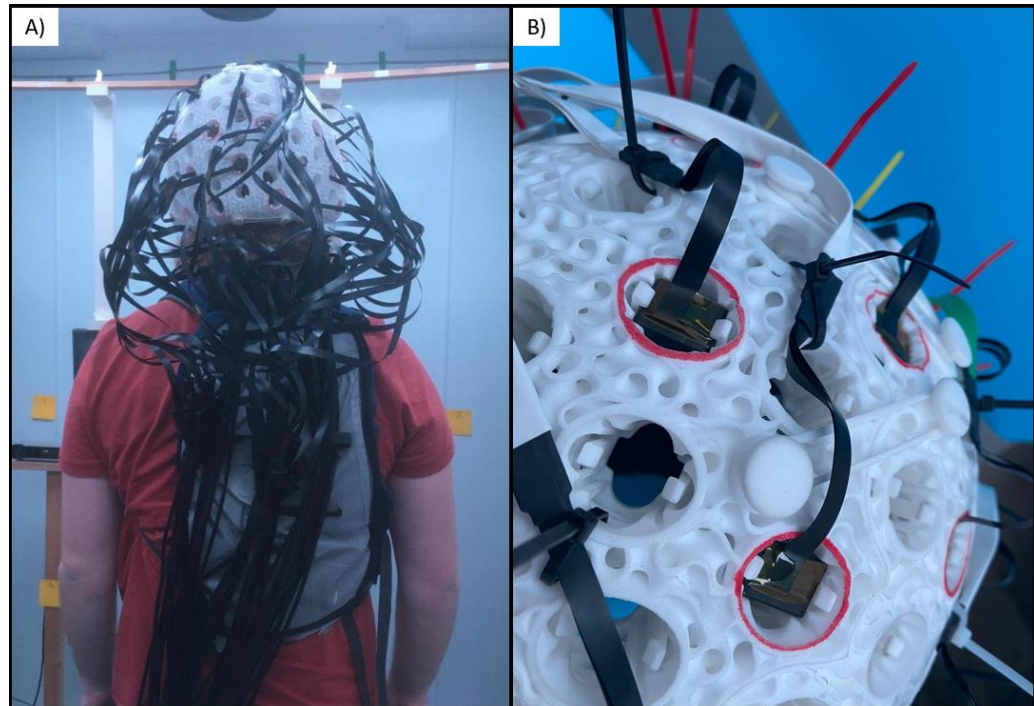


Figure 6.8: Cable management solutions. A) Cables are supported by the backpack. B) Cables are immediately tied to the helmet/cap to prevent the cables from pulling on internal sensors components.

6.7.2 Cable crosstalk

Each OPM uses coils to resistively heat the vapour cell to the correct temperature ($\sim 150^\circ\text{C}$). The frequency at which the current is applied to these coils is $\sim 400\text{ kHz}$, way outside the bandwidth of the OPM ($\sim 100\text{ Hz}$). However, these frequencies are generated independently by the electronics controlling each sensor. This means that, if all OPMs use the same heater frequency value, small discrepancies between each sensor's internal clocks can lead to differences of several Hz between each sensor. This leads to a beat effect due to the constructive and destructive interference between the two signals, where the beat frequency is the difference of the two signals. These beat frequencies do fall within the bands of interest in MEG. In order to prevent beat

frequencies affecting the data, the individual heater frequencies are spaced apart in intervals of hundreds of Hz such that the beat frequencies are also outside the bandwidth of the MEG measurement. However, as more and more sensors are added to the array, the beat frequencies are produced by more complicated superpositions of heater frequency signals. This makes it increasingly difficult to find a separation value that puts all possible beat frequencies out of the 0-100 Hz range. Figure 6.9a and b show examples of a typical noise spectrum with a noise spectrum with no heater frequency intervals (a), and a noise spectrum with heater frequency intervals of 427 Hz (b). As shown, significant artefacts appear in the signal which would obscure real MEG signals.

Here we modified the electronics to solve this issue. Differences in heater frequencies were eliminated by using a single external clock for all sensors, rather than individual internal clocks. The sensor electronics were modified so that the master unit provides the heater frequency signal for all sensors, which is passed through the modulation cables down the chain of sensors. The resulting noise spectrum is shown in Figure 6.9c.

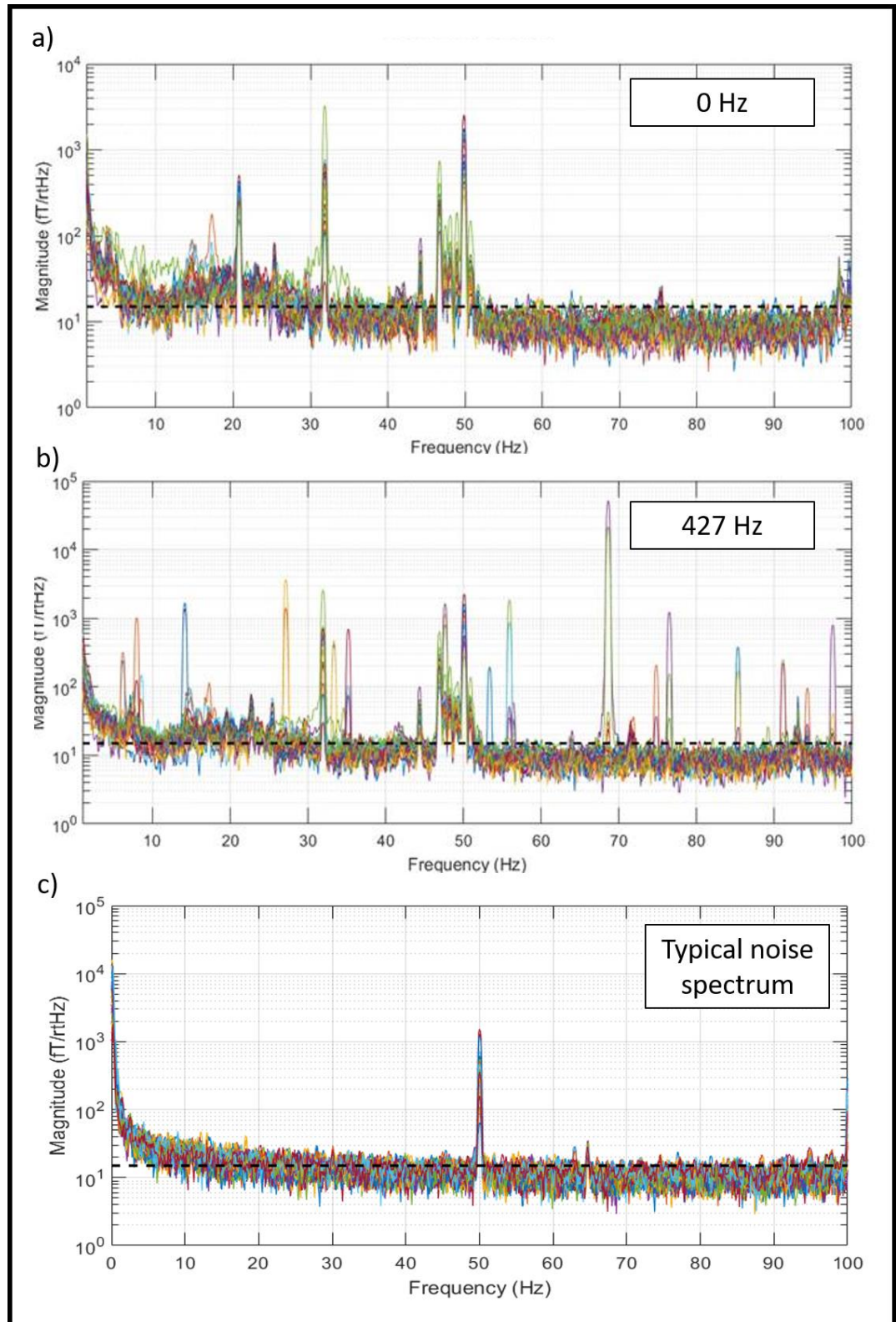


Figure 6.9: Noise spectra with heater frequency issues. (a) Noise spectrum when using internal clocks and heater frequencies are all the same value. (b) Noise spectrum when using internal clocks and heater frequencies are separated by 427 Hz. (c) A typical noise spectrum when using an external clock for heater frequencies.

Unfortunately, there is another source of interference from the cables moving relative to each other. Bringing cables into close proximity to one another, and specifically allowing that proximity to change during a measurement, introduces variable cross-talk between measurements. This is most likely to be a capacitive coupling effect (the mutual coupling of the electric fields of two nearby conductors) between the cables. The arrangement of the individual wires on the 60-cm flex cable leads to electric field patterns that interfere as cables move over one another as shown in Figure 6.10A. However, the capacitive coupling effect can be prevented by covering each cable in two layers of electrical insulation tape (Figure 6.10B). This not only better insulates the electric field from each cable, but it also slightly increases the distance between the cables, which reduces the effect. Figure 6.10C demonstrates the artefact produced when two bare OPM cables are laid over one another and periodically rubbed against each other. This represents a worst-case scenario as the wires are typically never pressed against each other, rather they glance off each other during a recording. Figure 6.10D shows the results for the same procedure when the two cables are taped. The artefact is greatly reduced (by a factor of ~ 4) even in this worst-case scenario.

So, in summary, a combination of modified electronics and modified cables helps us to reduce artefacts caused by operating large number of sensors simultaneously.

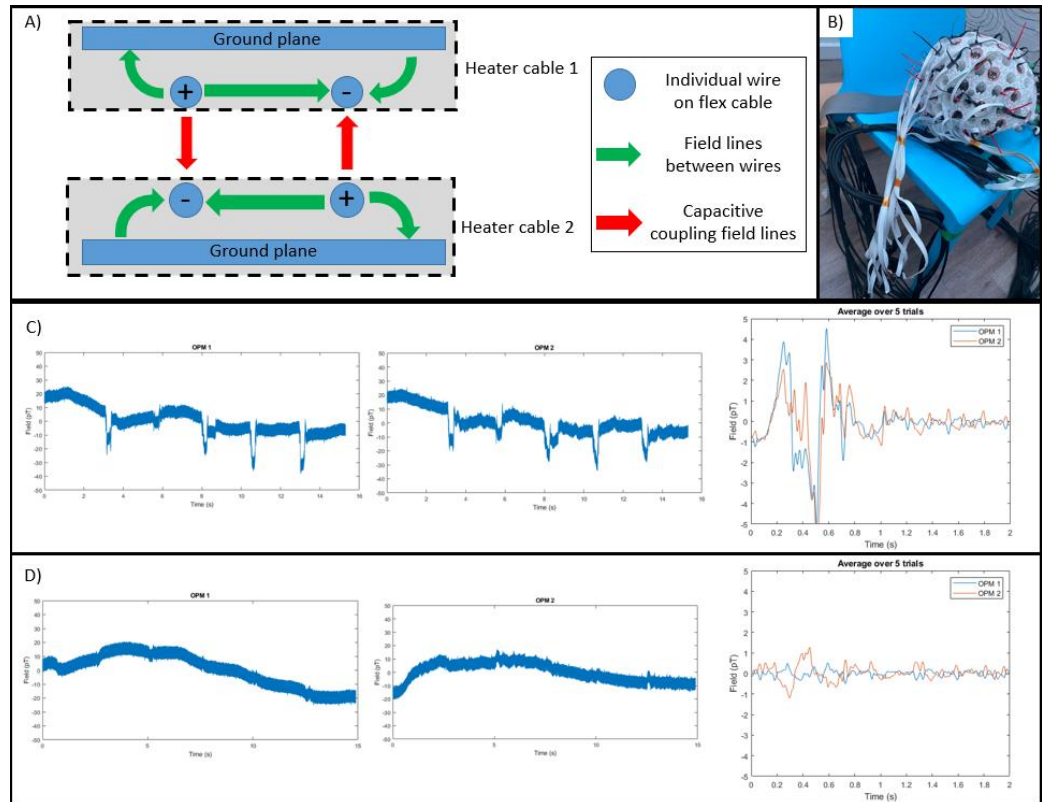


Figure 6.10: Capacitive coupling between flex cables. A) An illustration of how the geometry of individual wires laid out on the flex cable can cause field lines which interact with other cables. B) Flex cables are covered with insulating tape to prevent capacitive coupling. C) Artefact produced when two bare OPM cables are periodically rubbed against each other. A trace for each OPM is shown, and the time-locked average of each trace over 5 trials. D) The same as in C but with the cables taped with a layer of insulating tape.

6.8 Conclusion

In this chapter, we have designed an OPM-MEG system with whole-head coverage. We explored the use of the bike helmet design, and found that while the principle could still be applied, the commercial bike helmet could not fully meet the requirements of a whole-head system. Instead we developed a 3D printed rigid helmet that could provide the features we needed. We then compared in simulation our new method of mounting OPMs on the head with a flexible cap manufactured by QuSpin. The flexible cap has the benefit of being more adaptable to the participant's head shape as well as being able to hold the sensors closer to the head, but with less coverage of the head. The rigid helmet has greater coverage of the head but the sensors are slightly further from the scalp in order to accommodate multiple head shapes. However, both designs offer better coverage than a 275-channel cryogenic system as well as

higher signal amplitudes because of the proximity of the sensors. In addition, we have demonstrated a new co-registration procedure for each design, with the co-registration error manifesting differently for each design (for the rigid helmet, the errors are uniform across all sensors, whereas with the flexible cap, the errors are random). Again using simulations, we contrast these co-registration errors to show that the rigid helmet offers a more accurate source reconstruction. Finally, we have discussed the challenges of building a whole-head array of OPMs and addressed the issues of cable management and cross talk between sensor cables. In the next chapter, we explore a practical application of the two designs. We will compare them to each other as well as to a state-of-the-art cryogenic system, and assess their ability to perform whole-head OPM-MEG.

Chapter 7: Multi-channel whole-head OPM-MEG

This chapter follows the previous by presenting a practical demonstration of the two wearable OPM-MEG helmets (flexible and rigid) that we have developed. By using a paradigm that elicits fluctuations in motor-beta and visual-gamma oscillations, we compare results from the two systems. We also make a comparison with a state-of-the-art cryogenic system (275-channel CTF). Whilst both of our helmet designs allow for high quality data to be collected, we argue that (in agreement with the simulations in the previous chapter) the rigid helmet offers a more robust option. In particular, in agreement with Chapter 6, we show significant advantages for reconstruction of field data into 3D images of changes in neuronal current. Using repeat measurements in two participants, we show signal detection for our device to be highly robust. Moreover, via application of source-space modelling, we show that, despite having 5 times fewer sensors, our system exhibits comparable performance to an established cryogenic MEG device. The methods and results presented in this chapter have been published in Hill et al., *NeuroImage* (Hill et al., 2020), alongside the results and methods from Chapter 6.

7.1 Introduction

In the last chapter, we designed a 49-channel OPM-MEG system with whole-head coverage. We developed two different methods for mounting the OPMs on the head, and a new co-registration procedure for each design. We also addressed the challenges that a larger sensor array presents in terms of cable management and crosstalk between cables. Our two helmet designs comprised: a rigid, additively manufactured helmet, and a flexible EEG-style cap. The rigid helmet offers greater coverage of the brain due to its ability to hold sensors over the ears and jaw, but at a reduced signal amplitude as sensors are held slightly away from the scalp to accommodate the differing head shapes and sizes of multiple participants. The flexible cap holds the sensors closer to the scalp as it can easily adapt to different head shapes, but at a reduced coverage as it can't be placed over the ears and jaw. In both cases, the theoretical signal amplitude and coverage is better than that offered by a 275-channel cryogenic system.

The two designs also differ in the way that co-registration error manifests. In the rigid helmet, all sensor locations relative to one another are known accurately a-priori, and so any error in co-registering the helmet to the head affects all sensors equally (therefore the errors are systematic). The flexible cap must have each sensor localised individually, therefore each sensor has its own associated error (i.e. random error). Because of this, we showed in simulation that (again in theory) the rigid helmet reconstructs sources with better accuracy than the flexible cap. This is likely due to the fact that the rigid helmet error results in all sensors being shifted in the same direction, and so, while the localisation may be in the wrong location, the modelled field will still look similar to the measured field. For the flexible cap, if sensor locations are randomly perturbed, the spatial signatures of the lead fields will be disrupted, and hence any modelled field will always be a poor match for measured fields.

In this chapter, we aim to extend the theoretical and design work of the last chapter by demonstrating the practical application of these two whole-head designs, and how they compare with each other and with a cryogenic system. We use the three systems (rigid helmet OPM-MEG, flexible cap OPM-MEG, and cryogenic MEG) to measure electrophysiological responses to a visuo-motor paradigm. Employing a ‘test-re-test’ experimental design in two participants (each scanned 18 times, 6 times per system) we compare the reliability of OPM-measured magnetic field data, and source-space (beamformer-reconstructed) functional images, to an established state-of-the-art SQUID system. We experimentally contrast the trade-offs between flexibility (which ensures OPMs are close to the scalp) and rigidity (which enables accurate knowledge of sensor locations for source reconstruction), and compare them to the simulations performed in Chapter 6.

7.2 OPM-MEG system description

The system is similar to that described in Chapters 4 and 5, however it now contains Gen-2 QuSpin OPM sensors. As before, the OPMs were mounted on the participant’s head (see below) but were connected via a 60-cm lightweight ($3.3 \text{ g}\cdot\text{m}^{-1}$) flex cable to a back-pack. Thicker cables are then taken from the backpack to the control electronics. This system better controls the torque on the head caused by the weight of the sensors. Analogue output signals were again fed from the OPM electronics to a National Instruments digital acquisition system (DAQ). Although OPMs can measure two orthogonal components of the magnetic field, we only measured the component of the magnetic field that was normal to the scalp surface in the experiments reported here. Importantly, prior to the start of any experiment, all OPMs were calibrated using the manufacturer established procedure (described in Chapter 3) to ensure a response of 2.7 VnT^{-1} . This procedure is extremely important since post acquisition source modelling is highly dependent on accurately calibrated sensors.

Another difference between this chapter and the studies presented in Chapters 4 and 5 is the magnetically shielded room (MSR). Here, our system is housed within a newly developed MSR which was designed and built specifically for OPM operation (MuRoom, Magnetic Shields Limited, Kent, UK) (see Figure 7.1A). This MSR, which comprises 2 mu-metal layers and a single copper layer, is equipped with degaussing coils (Altarev et al., 2015), and this, coupled with its novel design, means that the background static magnetic field can be reduced to $\sim 1.5\text{nT}$, with field gradients of less than $2\text{ nT}\cdot\text{m}^{-1}$. For comparison, the Vacuumschmelze MSR used in Chapters 4 and 5 used 2 layers of mu-metal and one layer of aluminium (based on a design typically used to house cryogenic MEG systems), and has a background field of $\sim 30\text{ nT}$ with gradients on the order of $10\text{ nT}\cdot\text{m}^{-1}$ (this room is not equipped with degaussing coils). A comparison of the field maps along the z-axis at the centre of each of these rooms is shown in Figure 7.1B. Control of background field for OPM measurements is extremely important: on-board coils enable cancellation of background static magnetic fields inside the OPM cell, and consequently operation in ‘high’ fields (up to 50 nT). However, operation is such that these coil currents are set at the beginning of an experiment and left unchanged during the recording. This means any movement of the OPM array (e.g. due to head movement) relative to the background field will alter the fields within the OPMs. The operational dynamic range of the QuSpin zero-field magnetometers (which we define here as the maximum change in field before gain errors become $>5\%$) is $\sim 1.5\text{ nT}$ (Boto et al., 2018). In an MSR with a background field of 30 nT , this would mean a head rotation of around 3 degrees is enough to generate a 1.5 nT field change, which would, in turn, cause a significant ($>5\%$) change in gain of the OPM. In our novel MSR, an OPM can be rotated through 360 degrees and still maintain gain error within 5% .

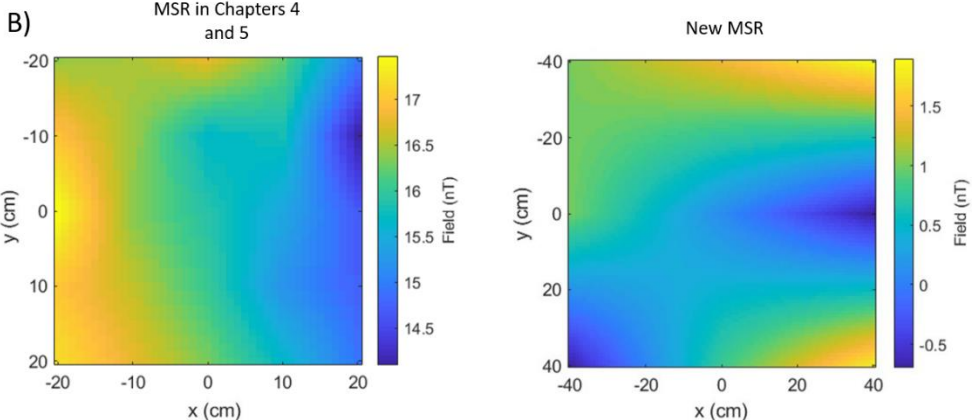


Figure 7.1: The MuRoom. A) A 3D render of the MuRoom and its construction. B) The magnetic field variation in z at the centre of the Vacuumschmelze MSR used in Chapters 4 and 5 (Left), and at the centre of the Magnetic Shields MSR used in the remaining chapters (Right). Note the change in the colour bar range, and the change in axis limits.

Even though OPMs remain operational in the low background field inside our MSR, head movement within this field still generates artefactual signals which can distort measured brain activity. For this reason, background field and gradients were further controlled using a set of bi-planar coils placed either side of the participant, the same as those used in Chapters 4 and 5 (Holmes et al., 2018; Holmes et al., 2019). These coils, which are wound on two 1.6-m square planes separated by a 1.5-m gap in which the participant is

placed, generate 3 orthogonal magnetic fields and 4 of the 5 independent linear gradients¹² within a (hypothetical) 40-cm cube inside which the participant's head is positioned. A reference array, placed behind the participant, then measures the background field/gradient and currents are applied to the bi-planar coils to cancel this remnant field. This takes the background field from 1.5 nT to ~0.5 nT, which enables a 3-fold improvement in suppression of movement artefacts.

A schematic diagram of the system is shown in Figure 7.2A. The participant sat on a non-magnetic chair placed in the centre of the MSR between the bi-planar coils (Figure 7.1B). Three separate computers controlled the OPMs, data acquisition, and the stimulus presentation. Note that all control electronics are kept outside the MSR in order to minimise the effect of magnetic interference on the MEG measurements.

¹² As the biplanar coils are generating magnetic fields in a space free of current sources, both the divergence and the curl of the field vector are zero. As a result, there are five independent spatial magnetic field gradients that can be generated in this space, of which our coils produce the three dominant terms in our MSR: $dB_x/dz(=dB_z/dx)$; $dB_y/dz(=dB_z/dy)$ and $dB_z/dz(=-2dB_y/dy=-2dB_x/dx)$.

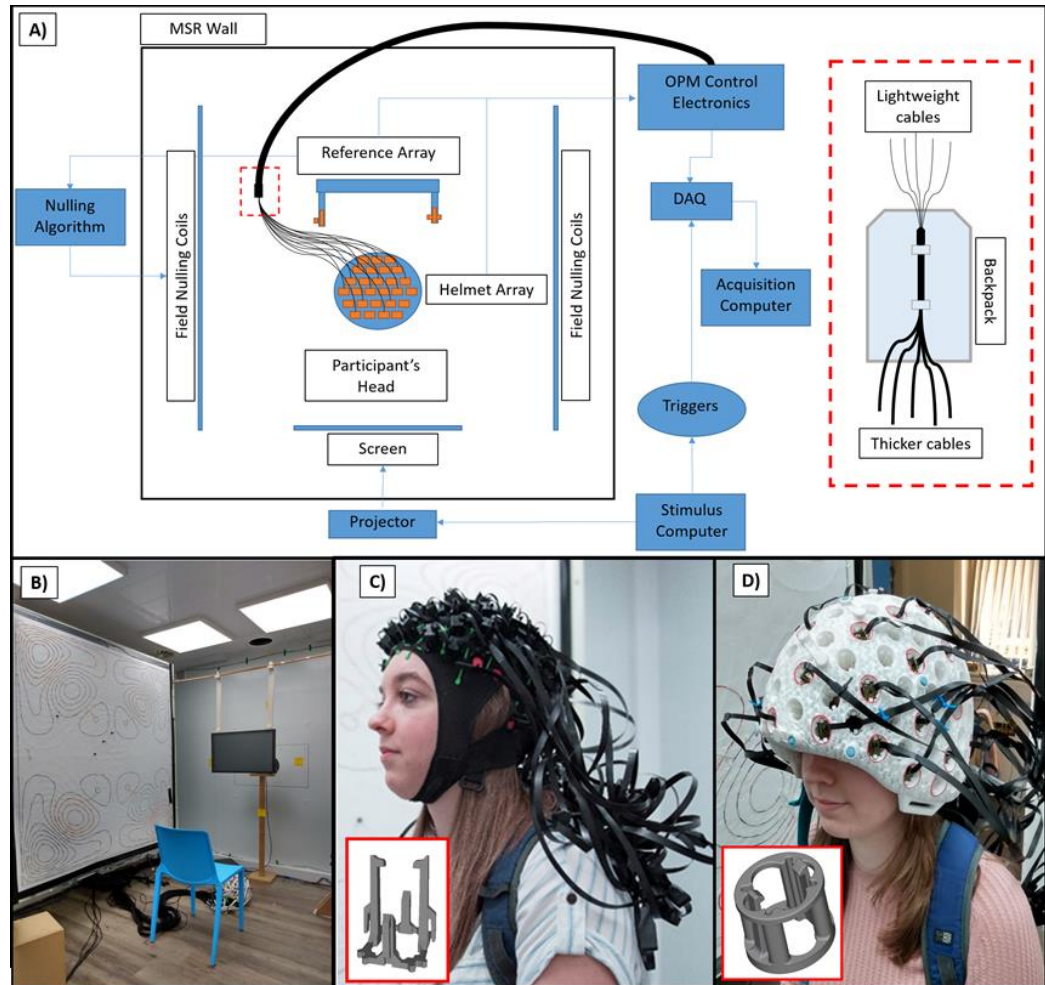


Figure 7.2: The OPM-MEG system. A) Schematic diagram of the whole system. B) Magnetically shielded room. C) Flexible (EEG style) cap. D) Rigid additively manufactured helmet. Both helmets contain push-fit clips to house the 2nd generation QuSpin OPMs (shown inset in C) and D)).

7.3 Experimental method

Two participants took part in the study (female and male, aged 29 and 24 respectively). Both were scanned 18 times; 6 times using OPM-MEG with the flexible helmet (*system 1*), 6 times using OPM-MEG with the rigid helmet (*system 2*), and 6 times using a cryogenic MEG instrument (*system 3*). Both participants gave written informed consent, and the study was approved by the University of Nottingham Medical School Research Ethics Committee.

7.3.1 Paradigm design

We employed a visuo-motor paradigm which comprised presentation of a visual stimulus which is known to robustly increase the amplitude of gamma oscillations in primary visual cortex (Hoogenboom et al., 2006; Iivanainen et al., 2019c). A single trial comprised 1 s of baseline measurement followed by visual stimulation in the form of a centrally-presented, inwardly-moving, maximum-contrast circular grating (total visual angle 5 degrees; 1.8 cycles per degree). The grating was displayed for a jittered duration of either 1.6 s, 1.7 s or 1.9 s. Each trial ended with a 3-s baseline period, and a total of 100 trials was used. During baseline periods, a fixation dot was shown on the centre of the screen. The participant was instructed to perform abductions of their right index finger for the duration that the stimulus was on the screen, in order to ‘activate’ primary motor cortex (where we expected to see beta-band modulation).

7.3.2 Data acquisition

We acquired data using our OPM-MEG systems with a sampling frequency of 1200 Hz. In the first participant, 42 sensors were available; in the second participant 49 sensors were available. In both cases, sensors were spread uniformly around the head in order to achieve whole-head coverage (as described in Chapter 6) with an average spacing of 48 ± 4 mm covering an approximate surface area of 840 cm² for the rigid helmet, and an average spacing of 36 ± 7 mm covering an approximate surface area of 482 cm² for the flexible cap. Visual stimuli were presented via back projection through a 21.5 cm diameter cylindrical waveguide in the MSR, onto a screen placed ~85 cm in front of the participant. We used an Optoma HD39Darbee projector with a refresh rate of 120 Hz. Temporal markers delineating the onset and offset of visual stimulation were also recorded by the DAQ. Co-registration was performed immediately after data collection (as described in Chapter 6.4).

Participants were free to move during the scan, but they were not actively encouraged to do so, and movement was not tracked.

Our cryogenic MEG recording used a 275-channel whole-head system (CTF, Coquitlam, BC, Canada), operating in 3rd order gradiometer configuration with a sampling rate of 600 Hz. Note that unlike our OPM system which solely employed magnetometers, the 275 sensors in our cryogenic system comprise 5-cm-baseline, axial gradiometers. These hard-wired gradiometers, coupled with 3rd order synthetic gradiometry, act to reduce background interference in the system, but at a cost of some depth sensitivity in the brain (Vrba and Robinson, 2001). Importantly, the fact that we use magnetometers in our two OPM systems and gradiometers in our cryogenic system makes it difficult to compare sensor-space measurements; this is addressed further below. Again, the stimulus was presented via back projection using a PROPixx (VPixx Technologies) data projector, onto a screen placed 95 cm in front of the participant. For the cryogenic system, co-registration was performed using head localisation coils and digitisation. Specifically, prior to MEG acquisition three head position indicator (HPI) coils were placed at the nasion and pre-auricular points. These coils were energized continuously throughout data collection to allow ongoing assessment of the head location. Following each experiment, a 3D digitiser system (Polhemus, Colchester, Vermont, USA) was used to record a 3D head shape for each participant, which included the locations of the HPI coils. Surface matching of the digitised head shape to a head shape extracted from the participants' MR images then allowed complete co-registration between brain anatomy and MEG sensor geometry.

7.4 MEG data analysis

We first bandpass-filtered all data between 1 and 150 Hz, and removed any 'bad' trials (specifically, trials in which the standard deviation of the signal at any one sensor was greater than 3 times the average standard deviation across all trials were removed). In order to visualise sensor space results, data

were then further filtered into the beta (13 – 30 Hz) and gamma (55 – 70 Hz) bands (note we also performed a post hoc analysis of the alpha band (8 – 13 Hz), with results given in Appendix 1). The Hilbert transform was taken and used to construct the analytic signal; the square of the analytic signal was then calculated to give the amplitude envelope (or “Hilbert envelope”) of oscillations in each band, for each sensor. This was averaged across trials, and baseline corrected (with baseline calculated over the $-3.4 \text{ s} < t < -2.5 \text{ s}$ time window, relative to stimulus offset at $t = 0 \text{ s}$). We then measured a sensor-space signal-to-noise ratio (SNR) for all channels: for the gamma band this was calculated as the mean signal in the $-2 \text{ s} < t < 0 \text{ s}$ window, divided by the standard deviation of the signal in the $0.5 \text{ s} < t < 1.5 \text{ s}$ window. For the beta band this was calculated as the difference in mean signals in the $-2 \text{ s} < t < 0 \text{ s}$ and $0.5 \text{ s} < t < 1.5 \text{ s}$ windows (i.e. the difference between the movement-related beta decrease and the post-movement beta rebound) divided by the standard deviation in the $-2 \text{ s} < t < 0 \text{ s}$ window. These SNR metrics were plotted across sensors to visualise the sensor-space topography of the beta and gamma responses. The mean envelope signals for the sensors with the highest SNR were also plotted.

Source localisation was performed using a scalar beamformer (Robinson and Vrba, 1998). The brain was divided into 4-mm cubic voxels and a pseudo-t-statistical approach used to contrast oscillatory power in an active window ($-1.2 \text{ s} < t < 0.3 \text{ s}$) and a control window ($0.6 \text{ s} < t < 2.1 \text{ s}$); this was then normalised by projected noise (Vrba and Robinson, 2001). Images showing the spatial signature of modulation in oscillatory power were generated for both the beta and gamma bands. Beamformer weights were calculated independently for each band; specifically, covariance matrices were generated using band-limited data and a time window spanning the entire experiment. This method was chosen as, by filtering the data into a narrower band prior to beamforming, the spatial resolution is increased because the beamformer no longer needs to suppress interference sources from outside the band of

interest. *[Note that, in some circumstances, narrowing the bandwidth leads to a less accurate characterisation of the covariance matrix. This is typically the case when the covariance is calculated over a short timescale (e.g. evoked responses), but as we are looking at an induced response over several seconds, this should not be an issue (Brookes et al., 2008)].* Covariance matrices were left un-regularised to maximise spatial resolution (Brookes et al., 2008). The source orientation for each voxel was obtained via a search for the highest reconstructed ratio of projected power to noise, and the forward solution was based on a single-sphere model. This algorithm was applied to all 18 experiments in both participants, yielding 18 separate images showing the spatial signature of oscillatory power change, for each band.

Based on the pseudo-t-statistical images, a peak location was determined, and a signal from this location was reconstructed. This was done in two ways: first, using data covariance calculated in the broad (1 – 150 Hz) band, beamformer weights were used to generate a broad-band ‘virtual sensor’ time course. A time-frequency spectrum was then constructed by sequentially frequency filtering the signal into overlapping bands, computing the envelope of oscillatory power, averaging over trials and concatenating in the frequency dimension. Second, using band-limited beamformer weights, the mean envelope signals in just the beta and gamma bands were constructed.

Based upon the derived source space images, source space time courses, and sensor-space data, we computed four summary metrics to estimate the effectiveness of each of our three MEG systems:

- **Test-re-test source-localisation consistency:** For each experimental run, we calculated the location of the peak in the pseudo-t-statistical image. These locations were averaged, and standard deviation measured in three orthogonal orientations to define an ellipsoid, spanning the spread of peak locations across runs. The volumes of the

ellipsoids were calculated as a summary statistic, with larger values indicating lower consistency of reconstruction.

- **Image consistency:** For each experimental run, the pseudo-t-statistical image was vectorised and Pearson correlation computed between all pairs of runs (i.e. for six runs this results in 15 separate correlation values). These were then averaged and the standard deviation was computed. Here, higher values would indicate greater consistency between runs.
- **Output SNR:** This was calculated based on trial-averaged, beamformer-reconstructed oscillatory envelopes. As for the sensor-space analysis, SNR was defined for the gamma band as the mean signal in the $-2 \text{ s} < t < 0 \text{ s}$ window, divided by standard deviation in the $0.5 \text{ s} < t < 1.5 \text{ s}$ window. For the beta band we calculated the difference in mean signal between the $-2 \text{ s} < t < 0 \text{ s}$ and $0.5 \text{ s} < t < 1.5 \text{ s}$ windows divided by the standard deviation in the $-2 \text{ s} < t < 0 \text{ s}$ window.
- **Output-to-input SNR ratio:** This is effectively a measure of the ability of a beamformer to reconstruct a signal. The measure is simply the SNR of the beamformer-reconstructed time course, divided by the SNR at the best MEG sensor. Values above 1 indicate the beamformer is improving data quality. Importantly, the beamformer not only requires high-fidelity data, but also accurate knowledge of sensor geometry (and consequently accurate co-registration). This simple measure therefore captures the effectiveness of the overall system. However, like input SNR, this is not comparable between cryogenic and OPM systems because a cryogenic system is based on gradiometers not magnetometers.

In all cases, summary statistics were computed independently for each frequency band and participant.

7.5 Results

7.5.1 MEG data – sensor-space comparison

Figure 7.3 shows sensor-space beta- and gamma-band signals. The topography plots show SNR with the six separate cases representing the six repeat measurements. The line plots show the trial-averaged oscillatory envelopes for the beta and gamma bands, extracted from the sensor with the largest SNR (all six runs are overlaid). Importantly, these results show very reliable repeat measurements for all 3 systems – the same sensors show the largest signal change for each run, and the oscillatory envelopes are highly repeatable. Specifically, in the beta band, in sensors over the sensorimotor areas, we observe the characteristic movement-related beta decrease (in the $-2\text{ s} < t < 0\text{ s}$ window) and the post movement beta rebound on movement cessation (in the $0\text{ s} < t < 2\text{ s}$ window). In the gamma band we observe the well-known synchronisation during visual stimulus presentation in sensors over occipital regions. These findings were robust across both participants - see Figure 7.8 in Appendix 2 for results in Subject 2.

Quantitatively, the SNRs are higher for the flexible cap than for the rigid helmet. This is to be expected as the flexible cap holds the sensors closer to the head, on average, than the rigid helmet. The SNR values for the OPMs and cryogenic sensors were comparable, however we note that such values should not, strictly, be compared. This is because cryogenic data are derived from 5-cm baseline axial gradiometers which are processed using third-order synthetic gradiometry based on an independent SQUID reference array; OPM data are completely unprocessed magnetometer data. Given that magnetometers exhibit greater sensitivity to distal sources, it is likely that they show greater contamination from environmental interference sources (including biomagnetic fields from the body and brain regions of no interest). Such environmental sources should be reduced significantly via gradiometry or reference array subtraction. However, the fact that SNR values are comparable

despite these differences speaks to the excellent performance of the OPM sensors. This topic will be addressed further in the Discussion.

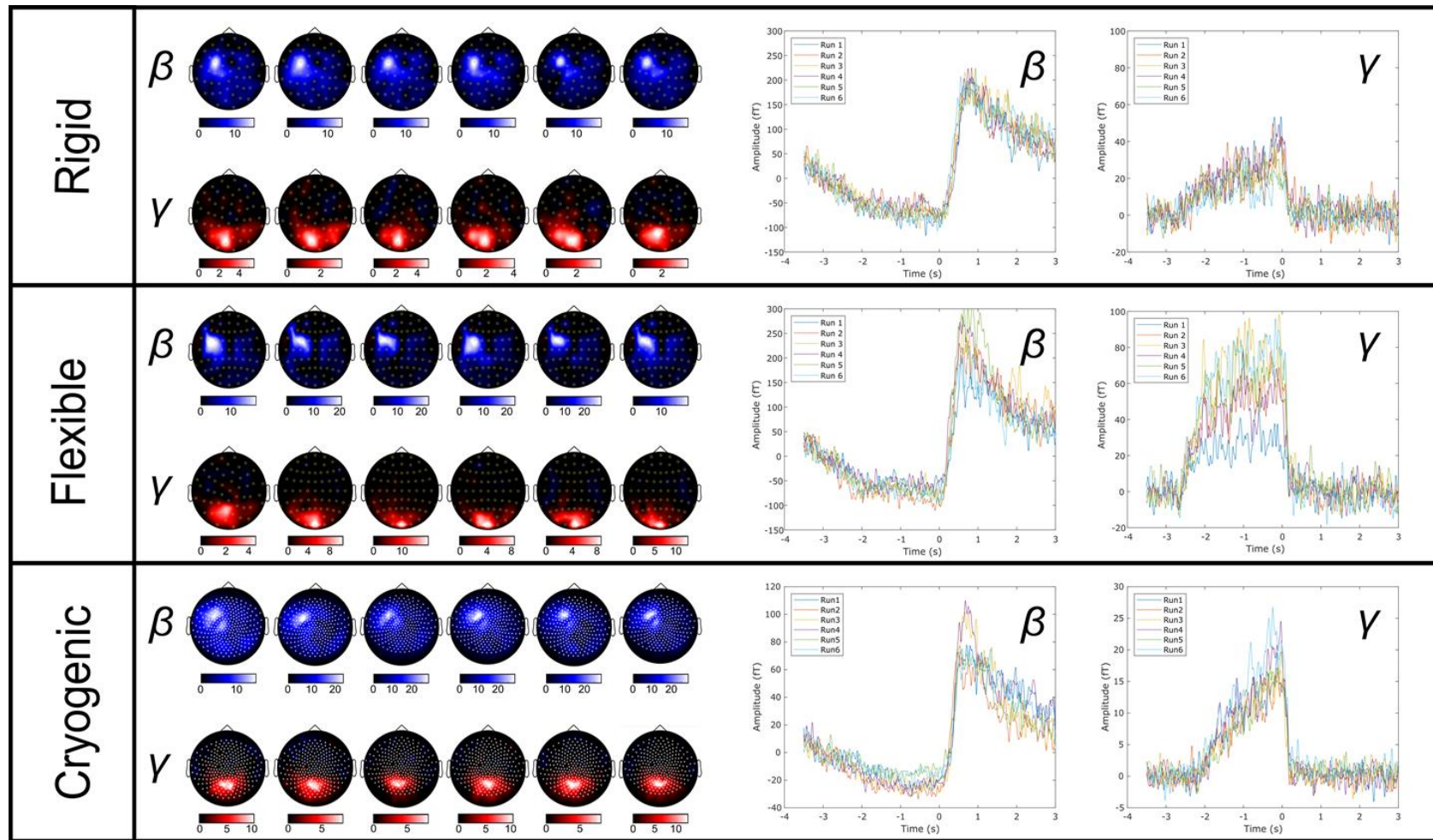


Figure 7.3: Sensor space results for Subject 1. Upper, middle and lower panels show results from the rigid, flexible, and cryogenic systems respectively. In all cases, the sensor space topography plots show estimated SNRs of the beta and gamma signals for each sensor; the six plots show six repeated measures in Subject 1. The line plots on the right-hand side show the oscillatory envelopes of the beta and gamma effects extracted from the sensor with the largest signal-to-noise ratio (all six runs are overlaid). An equivalent Figure for Subject 2 is shown in Appendix 2, Figure 7.7.

7.5.2 Source-space comparison and summary statistics

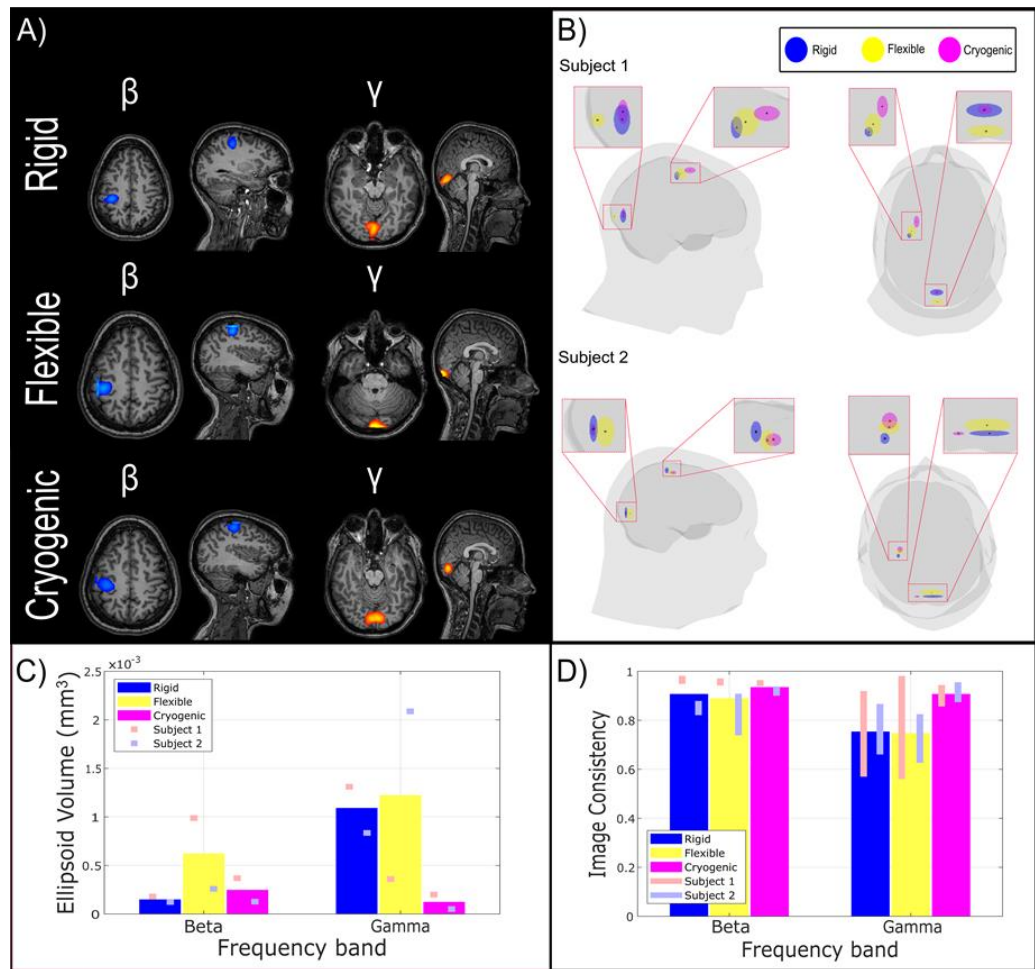


Figure 7.4: Spatial signature of beta and gamma responses. A) Beamformer pseudo-T-statistical images averaged over all 6 experimental runs for Subject 1. B) Glass brain, with the centre of the ellipsoids showing average peak location across runs. The size of the ellipsoids represents the standard deviation of the peak locations – and hence random variability of localisation across runs. C) Ellipsoid volumes averaged across participants. D) Image consistency (correlation between pseudo-T-statistical images) collapsed across both participants.

Figure 7.4 shows the results of source localisation. Figure 7.4A shows the spatial signature of the change in beta and gamma oscillations for all three systems. Results are for Subject 1, and the equivalent data for Subject 2 are shown in Figure 7.9. The pseudo-T-statistical images are averaged over all six experimental runs. As expected, for both participants, beta change maps to contralateral primary sensorimotor cortex and gamma modulation originates in primary visual cortex. In Figure 7.4B, the centre of each ellipsoid represents the mean location of the peak in the relevant pseudo-T-statistical images for beta or gamma modulation. The size of the ellipsoids represents the standard

deviation of the peak locations (measured independently in three orthogonal axes). In this way, the ellipsoid volume is a means to estimate the repeatability of source localisation, with lower values indicating a high repeatability. Ellipsoids for the rigid helmet are shown in blue, the flexible cap in yellow, and the cryogenic system in pink. Results for Subjects 1 and 2 are shown in the upper and lower panels, respectively. Note that the ellipsoids fall close to one another and are well localised to primary sensorimotor and visual regions. Figure 7.4C displays the ellipsoid volumes for both beta and gamma modulation. The bars in the bar chart show averages (across both participants) whilst the red and blue squares show the results for each of the two participants separately. Figure 7.4D shows the image consistency metric (that is, correlation of pseudo-T-statistical images for different pairs of experimental runs, where high values represent high consistency across runs). Again, the bars show average values, whilst the red and blue lines show the case for each participant (the lines are centred on the mean for that participant and the line length shows standard deviation).

Broadly, the repeatability of localisation for all systems is good. Test-retest localisation results are robustly localised within a small volume, and in all cases correlation between images from separate but identical experiments in the same individual are 75% or better (>90% in beta band). It is noteworthy that these source-localisation metrics characterise both the fidelity of the MEG data, and also the robustness of co-registration. In the beta band we observe comparable performance for all three systems, whilst for the gamma band, the cryogenic system remains somewhat more reliable. It is also noteworthy that the performance of the rigid helmet appears to be marginally better than the flexible helmet. Appendix 1 shows results for the alpha-band.

Figure 7.5A shows beamformer-estimated source time courses for the three different systems. The line plots show oscillatory amplitudes in the beta and gamma bands (for all 6 runs overlaid), whilst time-frequency spectrograms

(which are averaged over runs) enable a broadband picture of neural oscillatory modulation. The left-hand column shows data extracted from the locations of peak beta modulation (i.e. motor cortex) and the right-hand column shows data extracted from the locations of highest gamma modulation (i.e. visual cortex). Figure 7.5B shows estimates of the source-reconstructed SNR for the beta and gamma bands. As before, the bars show the average across participants, whilst the lines show the mean and standard deviation for each participant individually. Note that high-fidelity data can be extracted for all three systems, with comparable SNR. The SNR in the gamma frequency band is somewhat higher for the cryogenic system compared with both OPM-based systems, however this is largely a result of lower input (sensor-space) gamma SNR in Subject 2 (see Appendix 1 for alpha results).

Finally, Figure 7.6 shows input (sensor-space) and output (source-space) SNR for the two OPM systems, respectively. In agreement with Figure 6.7 (coverage figure in Chapter 6), the sensor-space SNR is larger for the flexible cap than the rigid helmet and this can be attributed to sensors being positioned closer to the scalp surface in the flexible cap and consequently picking up more signal. However, in source space, the SNR of the two systems is comparable. Figure 7.6 (Right) quantifies this behaviour by showing the ratio of output to input SNR; values greater than one indicate that application of beamforming is improving data quality by accurate reconstruction, and rejection of signals of no interest that do not originate from the probed brain location. In both systems, beamforming had a positive impact on SNR for both beta- and gamma-band data. However, this impact was more marked in the rigid helmet with e.g. SNR being approximately 2.5 times greater in source space, compared to sensor space, for the gamma band (compared to 1.5 for the flexible cap). This suggests that the beamformer is more effective in the rigid helmet than the flexible cap – such behaviour is in agreement with the results of simulations presented in Chapter 6 (Figure 6.6).

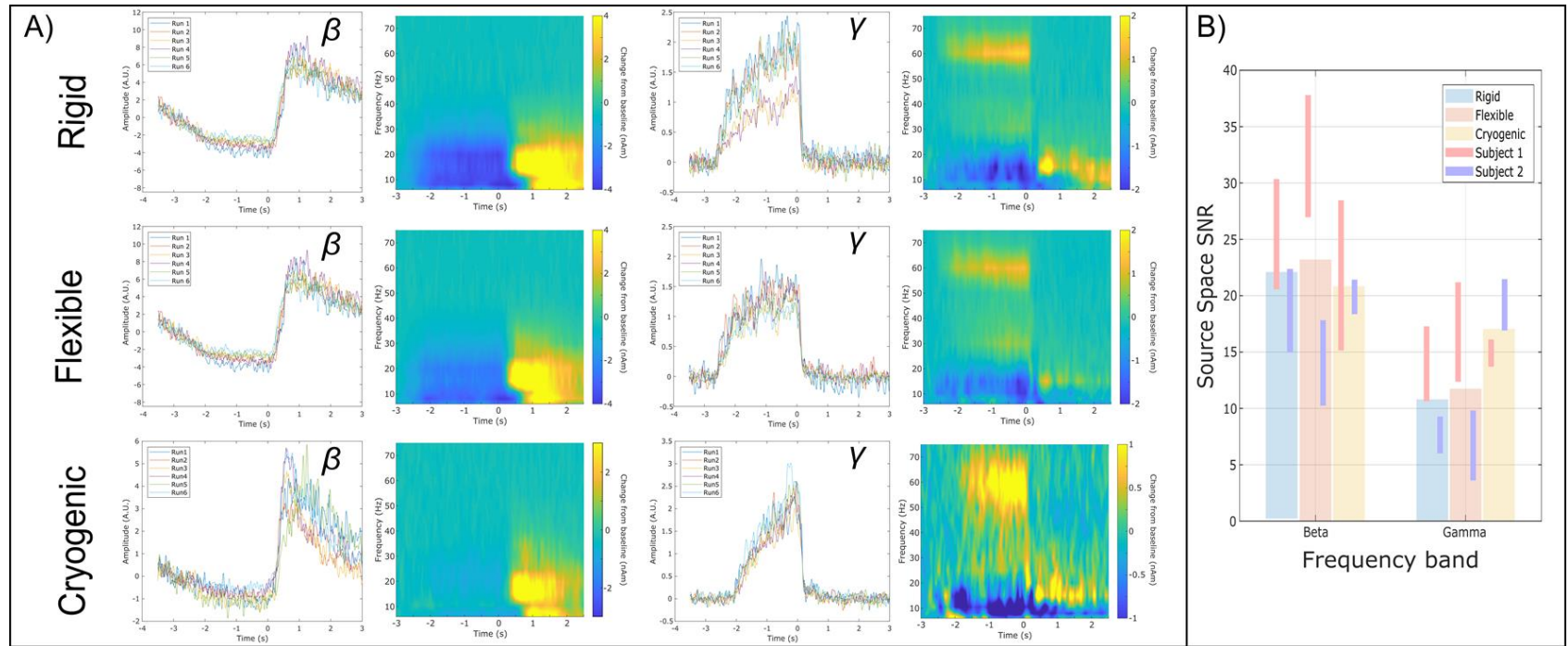


Figure 7.5: Beamformer-estimated (source space) neural oscillatory activity. A) Oscillatory envelopes and time frequency spectra extracted from the locations of peak beta (left) and gamma (right) modulation. Top, centre and bottom rows show rigid, flexible and cryogenic systems respectively. B) Signal-to-Noise Ratios for the three different systems in the beta and gamma bands.

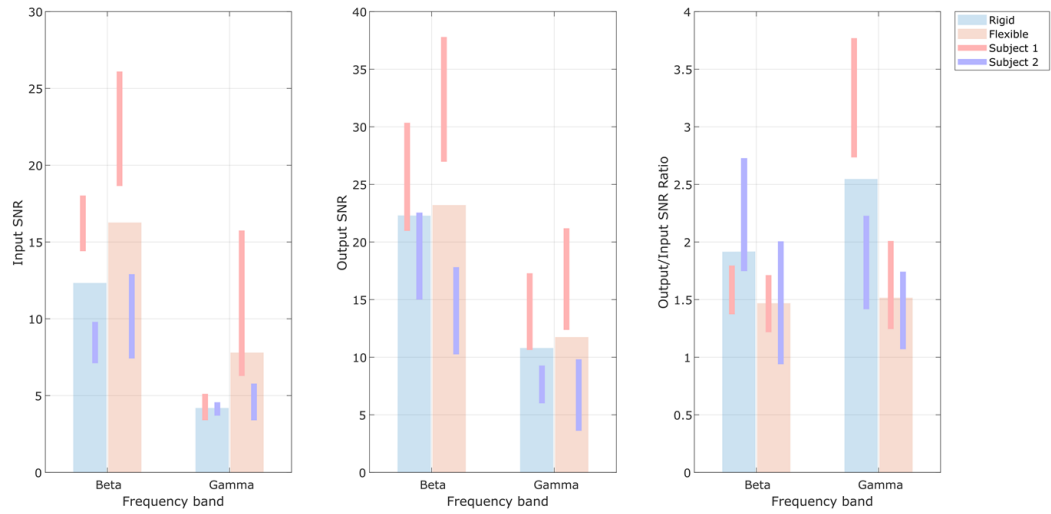


Figure 7.6: Helmet design comparison. (Left) Input SNR at the best sensor. (Middle) Output SNR measured in beamformer projected data. (Right) Ratio of output to input SNR.

7.6 Discussion

In this chapter, we have provided a practical demonstration of the two whole-head helmet designs presented in Chapter 6. We compared the performance of both systems with each other as well as with a 275-channel cryogenic system, while measuring motor beta and visual gamma oscillations. We have addressed the practicalities of each design, the quality of both the sensor-space data and the source-space data, as well as the repeatability of these. We will first discuss the comparison of the two helmet designs, followed by the comparison to the current state-of-the-art cryogenic system, and ending with the challenges that still remain.

7.6.1 Helmet design

Both designs are generic, fitting multiple individuals, and both have technical advantages/disadvantages. The sensors are held closer to the head in the flexible cap, and so pick up larger MEG signals than in the rigid helmet, as a consequence of the inverse square relationship between magnetic field and distance from the source. As expected therefore, our results showed that sensor-space SNR (Figure 7.3) was higher for the flexible compared to the rigid

helmet – particularly for Subject 1 where, for example, gamma band SNR was more than doubled in the flexible helmet [that said, in Subject 2 gamma SNR was not significantly different between the flexible and rigid helmets, the likely reason is that the shape of the flexible cap was distorted by the participant's hair, which pushed the sensors away from the scalp over the occipital regions].

The findings from the simulations in Chapter 6 (that a rigid system with systematic co-registration error outperforms a flexible system with random co-registration error) are supported by experimental results: the source-to-sensor-space SNR ratio (Figure 7.6 (Right)) is consistently higher for the rigid helmet compared to the flexible helmet, indicating that the beamformer was better able to reconstruct the source accurately. So, whilst the sensor space SNR was greater for the flexible cap, source-space modelling was better when the rigid helmet was used. This reflects the fact that, like for the bike helmet used in earlier chapters, rigidity of the helmet means accurate knowledge of sensor locations and orientations.

There are also practical considerations relating to helmet design. The flexible cap is lightweight (309 g) and adapts to any head size and so provides a comfortable experience for the participant. The rigid helmet is heavier (1.7 kg)¹³, more cumbersome, and less adaptable. That said, one advantage of the rigid helmet is that the OPMs are enclosed within a solid structure and therefore protected; future iterations of the helmet could also be made to better manage and protect cables. This all makes the system more robust, and is likely to be extremely useful in subject groups (e.g. infants) who might try to interfere with the sensors or cables during a scan. It is easy to see how our initial prototype could be made lighter (1.7 kg remains too heavy for effective

¹³ For comparison, the bike helmet with 81 Gen-2 sensors could ostensibly weigh as little as 500 g, but this does not account for any mechanisms to hold the sensors in place, and the bike helmet would be considerably less structurally rigid.

use), and adaptability could be enabled either via the introduction of multiple helmet sizes, or through the addition of a mechanism to allow sensor travel (in the radial orientation) within the helmet (whilst maintaining accurate knowledge of their location) similar to Zetter (Zetter et al., 2019). Another concern is usability. In the flexible cap, all sensors must be removed prior to co-registration. This is because with sensors in place, optical co-registration was ineffective because of the convoluted surface. Removal and replacement of all sensors between experiments was found to take more than an hour. However, for the rigid helmet, sensors can remain in place during co-registration making repeat measurements quicker. Finally, a flexible helmet allows some motion of the OPM sensors relative to each other during a scan (e.g. if a participant moves), whereas a rigid helmet holds them fixed relative to each other. Any movement within a background field generates artefacts. If sensors are rigidly held and helmet motion tracked, those artefacts would be well characterised and, in principle, could be modelled and removed. However, it would be much harder to track independent motion of all sensor locations and orientations. This therefore offers another potential advantage of a rigid helmet.

In summary, findings indicate that whilst the flexible helmet is comfortable to wear, aesthetically attractive compared to the rigid helmet, and works reasonably well, we believe that the better source-space modelling, ease of use, and system robustness make a rigid helmet a better option for OPM-MEG. The advantage of the rigid helmet would be reinforced by the availability of several helmet sizes or a facility for sensor travel to ensure close proximity of the scalp and the sensor.

7.6.2 Comparison with existing state-of-the-art

The potential advantages of OPMs over cryogenic MEG systems have been described in previous chapters – adaptability to different head shapes/sizes, motion robustness, no reliance on liquid helium, higher signal

strength, higher spatial resolution and lower cost. Not all of these potential advantages have yet been realised, but our data show that an OPM-MEG system, with even a modest sensor count (49), can compete with the current cryogenic MEG devices – at least for simple paradigms inducing alpha, beta and gamma responses. Our sensor space data (Figure 7.3) show the expected increase in signal strength by moving OPMs closer to the scalp compared to cryogenic flux transformers (beta band signals were, on average ~3 times larger; gamma band signals ~4 times larger, for Subject 1). However, SNR measures for the SQUID and OPM data are similar, and there are several reasons for this. First, the inherent noise level in our OPMs is higher than in the SQUID sensors, which means that whilst moving sensors to the scalp surface affords a signal increase, this is (in part) negated by increased noise. Our previous results from a single (static) OPM show an SNR increase of a factor of two (Boto et al., 2017). However, this assumes sensors touching the scalp and both head and sensor are immobile. Our rigid helmet does not fit perfectly to all participants, and with our flexible cap, participant's hair distorts the cap shape. This means that the expected increase in SNR compared to a cryogenic device will not necessarily be achieved completely. Second, we have used a wearable device that allows the participant to move freely. Although here the participant was not encouraged to move, slight movement of the head will cause a degree of low amplitude interference. Similarly, there is a known issue with interference caused by relative motion of cables adding to interference (as discussed in Chapter 6). Whilst we tried to minimise this using the procedures described, it still may affect output signals. Both issues can be readily solved by better field nulling (itself a topic of ongoing work) and modifications to sensor electronics. However, the present data were likely negatively impacted by these effects, lowering the OPM-SNR. Finally, as noted above, when comparing sensor-space SNR, we are comparing gradiometer data processed using synthetic gradiometry (cryogenic system), to completely unprocessed magnetometer data (OPMs), with the latter being more sensitive to interference. With these three considerations taken into account, it is

encouraging that OPMs show similar performance to the established SQUID-based sensors.

A much better comparison of OPM- and SQUID-based MEG can be achieved via metrics of system performance in source space. Here, test-re-test source localisation showed that pseudo-T-statistical images were extremely repeatable: for all three systems, sources were localised as expected to primary sensorimotor and visual cortices. There were some (small) differences between locations across the three systems and (as with all neuroimaging experiments) a limitation here is that we have no access to “ground truth” and therefore it’s impossible to know which system provides the most accurate localisation. Differences in localisation could be brought about by a number of effects, including technical aspects such as co-registration or calibration accuracy, and also changes in the paradigm set up (see below). Nevertheless, these differences were small. Ellipsoid volumes, detailing the spread of peak locations across experimental runs within a system were highly comparable for both the rigid helmet OPM and cryogenic systems for the beta band. Likewise, our image consistency metric showed better than 90% correlation across runs for all 3 systems. Gamma band results, in both participants, were a little more variable for OPMs compared to the cryogenic system with, on average, larger ellipsoid volumes and lower repeatability. There are likely two reasons for this: first a lower sensor space SNR due to the proximity of the sensors to the head, and second, limited sensor coverage (particularly in the flexible cap) over the visual cortex. Nevertheless, gamma band signals were robustly localised to primary visual cortex and functional images were >75% reproducible.

Perhaps the best measure of MEG system fidelity is source space SNR. This is not plagued by the magnetometer/gradiometer comparison problems that affect sensor space SNR. Moreover, it combines information across channels and requires effective magnetic field modelling, and hence high accuracy of co-registration, as well as high quality input data with well

calibrated sensors. In this way it is a good marker of fidelity of the whole system, rather than just of the OPM sensors. Here, again, we showed that source space SNR for the OPM and cryogenic systems were comparable. In the beta band, OPMs showed marginally (but not significantly) improved SNR; in the gamma band, the cryogenic system had better SNR although this was mostly driven by Subject 2; in fact across all experimental runs in Subject 1, gamma band SNR was similar for all three systems. It is important to recognise that source localisation optimally combines information across sensors in a weighted average; it is well known that the more sensors that are available, the better source localisation performs (Boto et al., 2016; Vrba et al., 2004). With this in mind, perhaps the most surprising result of this study is that source localisation is comparable between OPM and cryogenic systems, despite the fact that the cryogenic system has more than 5 times more sensors. However, this appears to support the theoretical findings by Tierney et al. (Tierney et al., 2019b). It is tempting to speculate that whilst, here, we have shown our OPM system to be “as good” as the current state of the art, as OPM systems inevitably gain more sensors, it is likely that they will significantly overtake cryogenic instruments.

We should point out that one limitation of the study presented relates to experimental conditions. We tried to match conditions as closely as possible across systems, however there were some unavoidable differences: first the viewing angle for visual stimulation was slightly different in the cryogenic MEG set-up than for the OPM systems because the participant was seated in a different posture. Second, finger abductions were performed with the hand resting on a surface, but the surfaces were different, potentially resulting in different sensory feedback. Third, for purely logistical reasons, it was not possible to match the times at which the participants were scanned; this introduces a caveat due to differences in responses depending on e.g. circadian rhythm (Wilson et al., 2014) or menstrual cycle (Sumner et al., 2018). All of the

above could add to variance in our data and consequently systematic differences in the responses measured.

7.6.3 Future challenges

An important consideration relating to our results is the difference between ‘physical’ and ‘effective’ sensor location/orientation. In the last two chapters, we have only described physical error – that is, how accurately we know the location and orientation of the sensitive volume of each OPM, relative to the brain. We have argued that this relates to the accuracy by which the helmet is built and the accuracy of the co-registration procedure used to localise the helmet on the head. However, other factors can mean that the physical orientation of a sensor (i.e. the orientation along which we expect to measure field) and the effective orientation (i.e. the real sensitive axis) can differ. The most obvious reason for this would be cross talk between sensors. During sensor operation, a modulation field – generated by on-board electromagnetic coils within an OPM – is applied to the rubidium vapour and it is the direction of this field that determines the measurement orientation. Although this field is strongest inside the cell, it spreads outside the OPM housing and as a result, will penetrate other nearby OPMs. Superposition of the fields from other OPMs can therefore change the orientation (and amplitude) of the modulation field within each OPM’s cell, meaning that the effective measurement orientation of the sensor will differ from its physical orientation. As a consequence, the forward field calculated using the sensor’s physical orientation would likely provide an inaccurate representation of real measurements. A similar effect occurs due to gain errors. Previous work (Boto et al., 2018) has shown that OPM gain depends on background field. Sensors are calibrated accurately at the beginning of any experiment and so we ensure a known gain. However, if the background field shifts during a measurement, the gain can change – a field shift of approximately 1.5 nT would result in a 5% gain reduction. Again, this means that the lead field would become inaccurate.

The beamformer (particularly with no regularisation) is extremely sensitive to errors in forward model, and in turn is dependent on accurate sensor orientation and gain calibration. Here, these problems were mitigated to a degree; separation of the sensors was relatively large and so cross talk was minimal. Further, field shifts were relatively low (<1.5 nT for all runs; average of $0.67 \text{ nT} \pm 0.32 \text{ nT}$ across all runs in both participants). However, as sensor arrays become denser, or are operated in a less stable magnetic environment, cross talk would require correction, and potentially we would need to use dynamic field stabilisation to prevent the gain changing throughout the experiment (Holmes et al., 2019). Finally, as noted above, small movements of sensors within the remnant background field generate low amplitude interference. In the last two chapters, we addressed some of these concerns – e.g. beating between heater signals was negated by driving the heaters on all OPMs with synchronised currents of the same frequency. However, most of these concerns mainly affect lower frequencies (e.g. delta band). This is, unfortunately, also where OPMs have an inherently lower performance (noise floor of $\sim 20 \text{ fT}/\sqrt{\text{Hz}}$ compared to $\sim 7 \text{ fT}/\sqrt{\text{Hz}}$ for $>10 \text{ Hz}$ for a SQUID). This means that low frequency measurements are more challenging for an OPM-based system. Nevertheless, improvements to electronics, better cable management, better field nulling, and ultimately improved OPM sensors will undoubtedly meet this challenge.

Finally, here we have shown an approximately equivalent performance of a 49-channel OPM system and a 275-channel cryogenic system, however it is important to also state that these were relatively simple paradigms with relatively few sources (motor and visual cortex) 'active'. It has been shown previously that effective beamforming can be carried out using 50 sensors (Vrba and Robinson, 2002). However, as the number of sources increase (e.g. for cognitive or resting state paradigms) a greater number of sensors may be required. In addition, higher sensor counts would mean a greater sensor density and consequently the array would be able to capture higher spatial

frequencies of field patterns on the scalp. These higher frequencies are potentially important for OPM-based systems which, because they are closer to the scalp, can sample higher spatial frequencies than would typically be measured in SQUID-based MEG. Indeed, in a recent study by Iivanainen et al. (Iivanainen et al., 2019a), the authors used a theoretical framework to suggest that on-scalp MEG recordings could significantly benefit from up to three times the sensor count of conventional systems, if they are to capture the highest spatial frequencies. It follows that moving to higher sensor density than our current 49-channel system would be highly beneficial.

7.7 Conclusion

In conclusion, we have shown that it is possible to construct a ‘whole-head’ wearable MEG system based on commercial OPM sensors, using two different approaches. Whilst both designs work well, we argue that the rigid helmet is a more judicious choice. At the sensor level, repeated measurements showed both OPM and cryogenic systems to be extremely reliable. In source space, despite 5 times fewer sensors, our OPM-MEG system showed comparable performance to the established state of the art in terms of source localisation reliability and output (source space) signal to noise ratio, in the alpha (see Appendix 1), beta and gamma bands. OPMs remain a nascent technology and significant technical challenges remain. Nevertheless, there are no fundamental barriers to combining large numbers of sensors.

Appendix 1: Alpha band summary

The same methodology as that described in our main manuscript was used to analyse responses in the alpha/mu band (these results are kept in an appendix in order to shorten and simplify the figures in the main body of the chapter). As for the beta and gamma bands, data were first frequency filtered to the 8-13 Hz band, and then processed using a beamformer approach. We derived pseudo-t-statistical images showing the spatial signature of the largest

alpha band changes, as well as our summary measures of ellipsoid volume, image consistency, sensor-space SNR and output to input SNR ratio.

Results showed that the largest changes were localised to sensorimotor cortices and probably reflect the well-known ‘mu’ rhythm (an 8-13 Hz oscillation generated by the sensorimotor system) (see Figure 7.7A). Some alpha changes were also noted over visual cortex. Summary statistics support the findings in the main chapter: localisations showed that pseudo-t-statistical peaks were largely overlapping for all three systems (Figure 7.6B), with ellipsoid volumes smallest for the rigid helmet (Figure 7.7C – left panel). Image consistency (Figure 7.7C – centre panel) was similar in all three systems for Subject 1, but better in the cryogenic system for Subject 2. Even though sensor space SNR was better for the flexible system (Figure 7.7D – left panel) source space SNRs were comparable for both the rigid helmet and the flexible cap, and for the cryogenic device (Figure 7.7C, right panel). As previously, we observed the output/input SNR to be higher for the rigid helmet compared to the flexible cap (Figure 7.7D – right-hand panel), a result of the improved knowledge of sensor location and orientation.

In summary, alpha-band findings strongly support beta and gamma results in showing the advantages of the rigid cap, and moreover that the OPM and cryogenic systems are comparable. This is of some importance due to the known degradation of performance at lower frequency. Specifically, OPM noise levels are higher at low frequency; further, movement artefact and relative cable motion will likely affect the lower frequencies. However, clearly performance of OPM-MEG is not limited down to 8 Hz. The delta and theta bands remain a topic of future research.

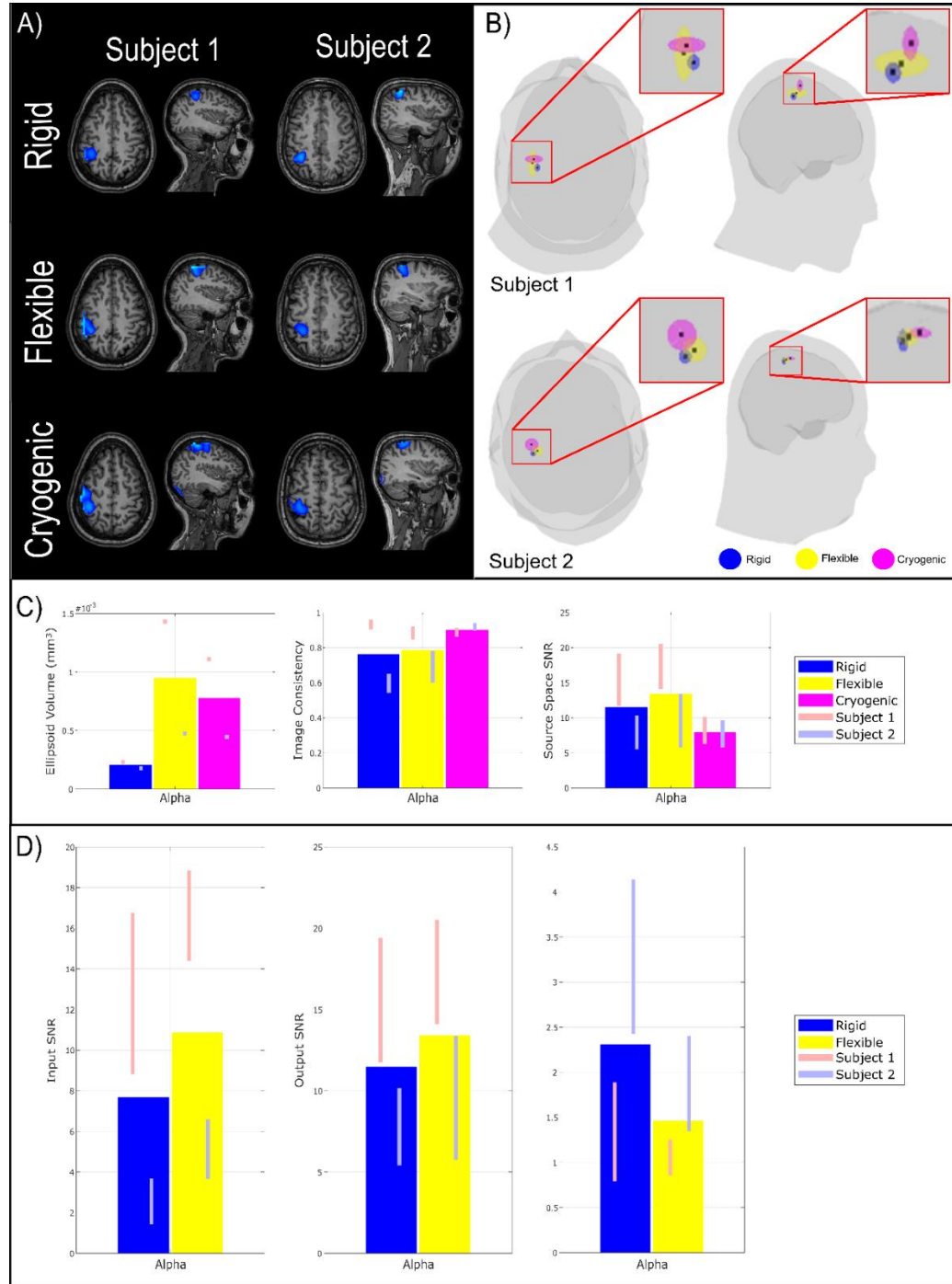


Figure 7.7: Summary of results in Alpha band. A) Beamformer pseudo-T-statistical images averaged over all 6 experimental runs for both participants. B) Glass brain, with the centre of the ellipsoids showing average peak location across runs. The size of the ellipsoids represents the standard deviation of the peak locations – and hence variability of localisation across runs. C) (Left) Ellipsoid volumes averaged across participants, (middle) Image consistency (correlation between pseudo-T-statistical images) collapsed across both participants, (right) Signal-to-Noise ratios for the three different systems in the alpha band. D) (Left) Input SNR at the best sensor, (middle) Output SNR measured in beamformer projected data, (right) Ratio of output to input SNR.

Appendix 2: Subject 2 results

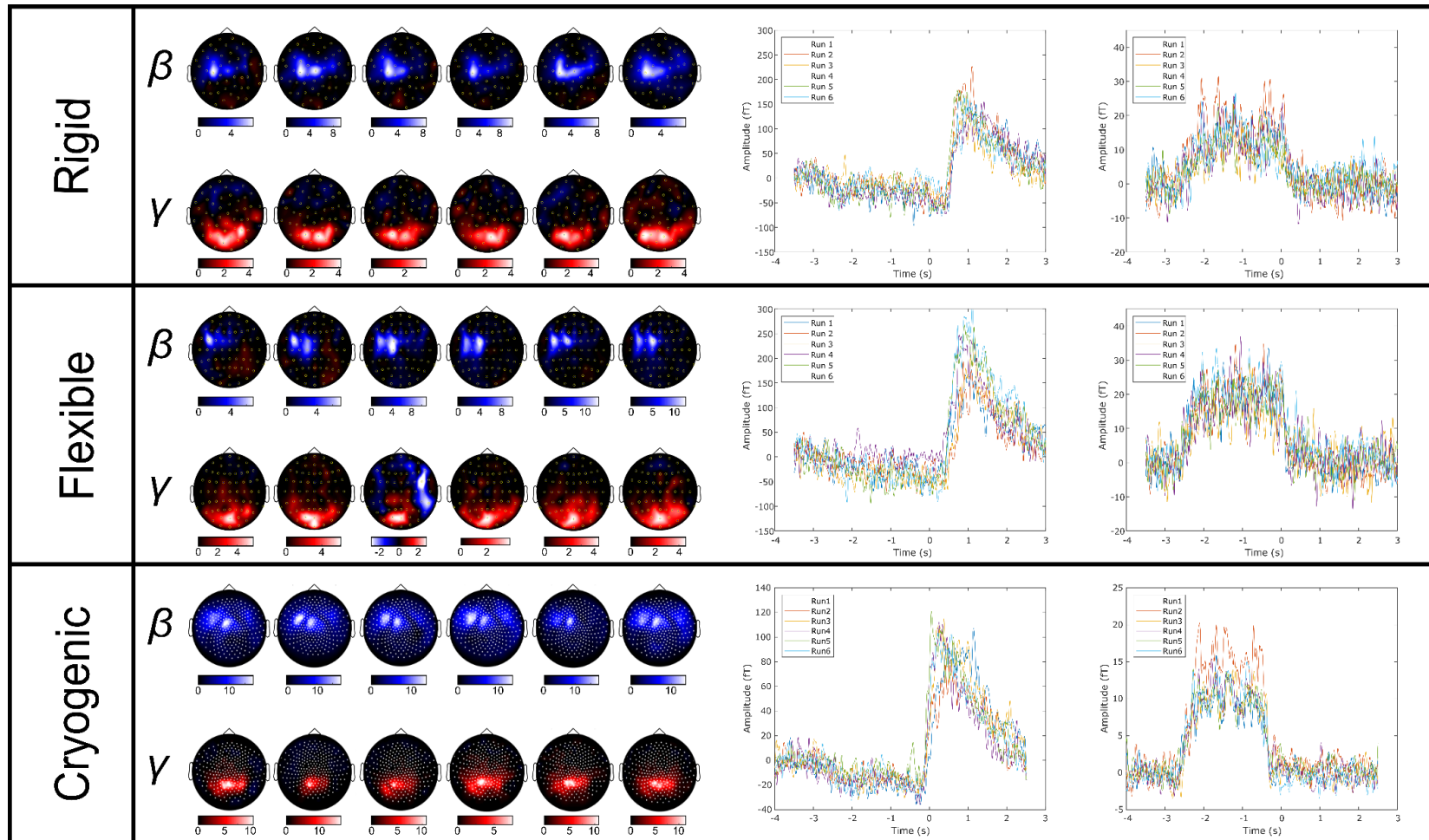


Figure 7.8: Sensor space results for Subject 2. Upper, middle and lower panels show rigid, flexible, and cryogenic systems respectively. In all cases, the sensor space topography plots show estimated signal to noise ratios of the beta and gamma signals for each sensor. The line plots show the oscillatory envelopes of the beta and gamma effects.

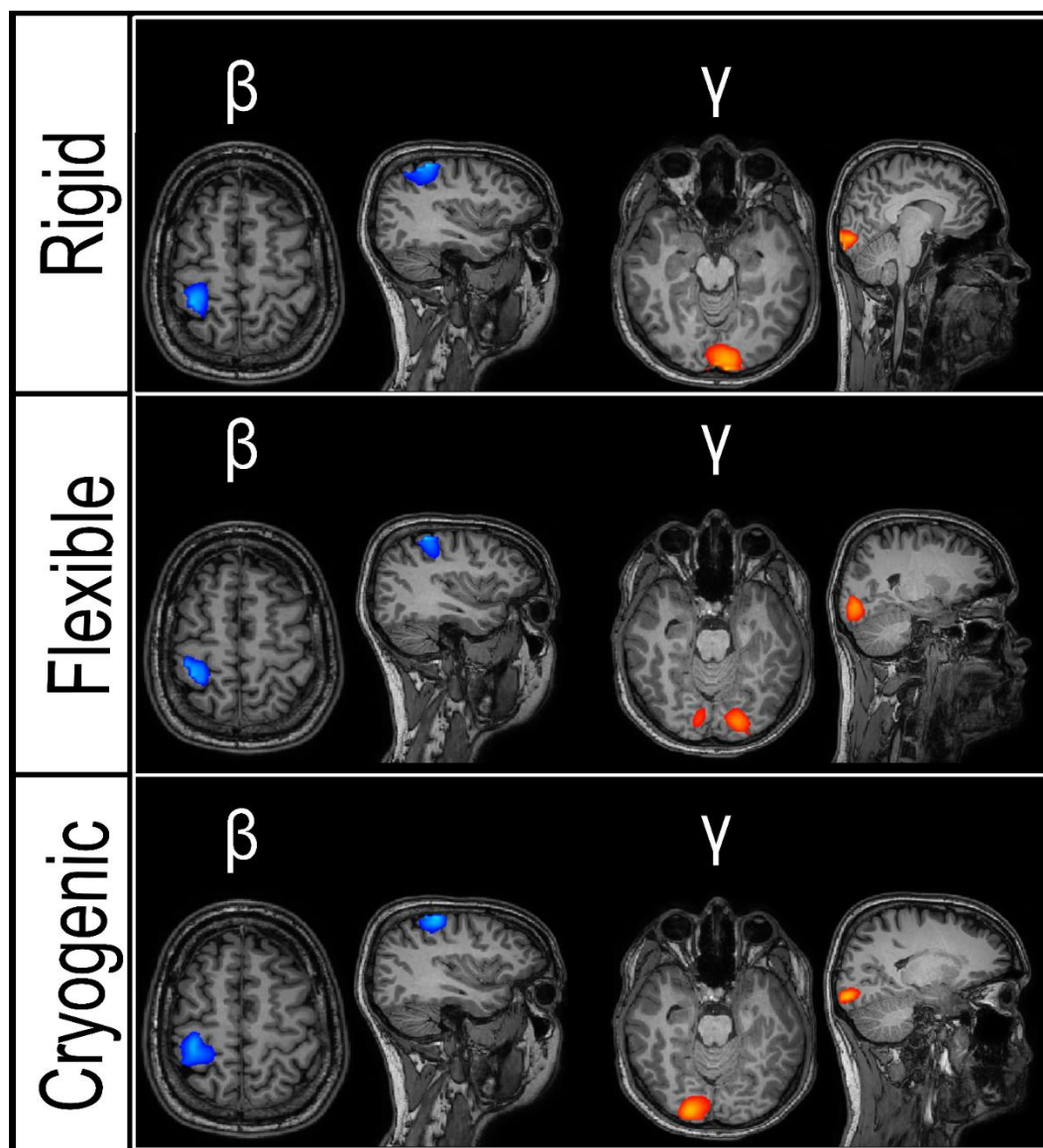


Figure 7.9: Beamformer pseudo-T-statistical images averaged over all 6 experimental runs. Results for Subject 2 shown.

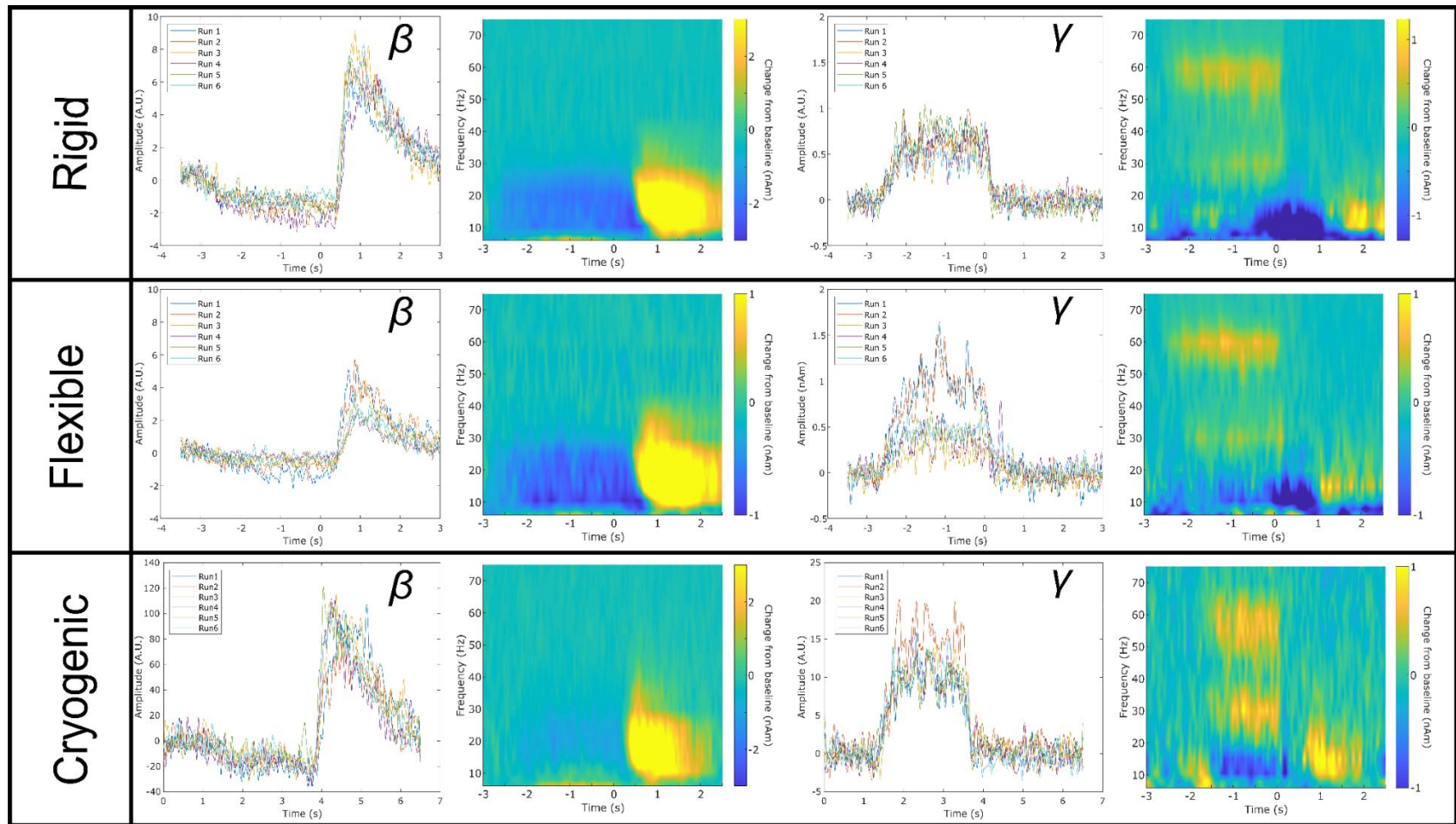


Figure 7.10: Beamformer estimated (source space) neural oscillatory activity in Subject 2. Oscillatory envelopes and time frequency spectra extracted from the locations of peak beta (left) and gamma (right) modulation. Top, centre and bottom rows show rigid, flexible and cryogenic systems respectively

Chapter 8: A naturalistic motor learning paradigm

In this chapter, we combine the work of the four previous chapters to demonstrate the performance of a 50-channel whole-head OPM-MEG system while performing a naturalistic motor learning paradigm in which a participant must move freely (an adaptation of the ukulele paradigm from Chapter 5). We develop a method for scoring a participant's performance whilst playing a short sequence of chords. We also use a more sophisticated motion tracking system to obtain accurate timings of the onset and offset of motion. We scan three adult participants 5 times each, on separate days using the natural motor learning paradigm, and we aim to assess how beta oscillations are modulated by success in the task. We find that an increase in beta modulation occurs in higher scoring trials (compared to lower scoring trials). This was significant in two of the three participants. We also assess functional connectivity, showing clear structure in the functional organisation of cortical regions during the task.

8.1 Introduction

In Chapter 5, we demonstrated the versatility of our prototype bike helmet system by scanning a participant while they played the ukulele. The task involved a participant, with no prior experience with the instrument, playing a 5-chord sequence (C, F, G, C, G). These chords were chosen specifically to increase in difficulty by involving 1, 2, and 3 fingers at a time. We successfully recorded electrophysiological data, showing that OPM-MEG technology could cope with a range of motions including: (i) rotating the head back and forth to look at the visual representation of the chords and the frets; (ii) moving the left hand to form the chords; and (iii) moving the right hand to strum the strings. Despite head (and hence sensor) translations and rotations >7 cm and $>30^\circ$ respectively, we were able to capture expected electrophysiological responses in both the beta and gamma frequency bands. This demonstration highlighted the possibility to implement a naturalistic motor experiment in which the neural substrates underlying motor learning are probed.

However, the demonstration in Chapter 5 was limited by the number of OPMs used and so only a fraction of the head was covered. There was also a significant issue of the weight of the Gen-1 sensors, particularly the cables causing torque on the head, making the experiment uncomfortable for long experimental durations. Over the last two chapters, we've developed a new system which uses smaller, lighter Gen-2 OPMs held inside a generic 3D printed helmet with whole-head coverage using ~ 50 sensors. By performing a relatively simple finger abduction task with simultaneous visual stimulation, we demonstrated the ability to robustly detect motor beta- and mu-rhythms as well as visual gamma, with comparable quality to a 275-channel cryogenic system. However, this new whole-head device is as yet untested in paradigms with large head motion.

In this chapter, we combine the naturalistic paradigm from Chapter 5 with the generic helmet and whole-head coverage from Chapters 6 and 7 to obtain pilot data for a truly novel MEG experiment. We measure and localise beta band modulation which we expected to see during the task. In addition, by exploiting having whole-head coverage, we also perform functional connectivity analysis between parcellated regions in the AAL atlas. As well as obtaining the electrophysiological data and performing source localisation, we also record and analyse audio data obtained while the participant is playing the instrument. This enables us to “score” their performance across individual trials. This will allow us to compare any changes in the beta response or functional connectivity to their performance in each trial. A sophisticated motion tracking system is used to track participant movements robustly, including the motion of each hand to provide more accurate timings of movement cessation at the end of each trial. We aimed to scan three participants 5 times each in order to gain insight into how participants learn the motor skills required to play the chord sequence. We aim to test three hypotheses: 1) *that our 50-channel whole-head system is as robust as our previous systems against participant motion, and so high fidelity MEG data can be obtained*; 2) *that the spatial resolution of our system will allow us to see asymmetry between the left and right motor cortices due to left fingers vs. right arm movement*; 3) *that beta modulation will differ systematically with performance on the task according to a predictive coding model of the beta rebound*.

8.2 Methods

Three participants took part in the study (1 female aged 30, and 2 males aged 26 and 40, all right-handed). Each participant was scanned 5 times each on separate days. All participants gave written informed consent, and the study was approved by the University of Nottingham Medical School Research Ethics Committee.

8.2.1 OPM-MEG system description

The OPM-MEG system was largely identical to the setup described in Chapter 7.2 using the rigid helmet, with only two key differences: 1) a microphone was placed at the back of the room to record the participant playing the ukulele, and 2) a motion tracking system, similar to that presented in Chapters 4 and 5 but with a more sophisticated arrangement (see Figure 8.1A) was used.

The motion tracking system used in these experiments was again an Optitrack system (NaturalPoint Inc., Corvallis). However, rather than using a single V120:Duo camera in front of the participant, five Flex-13 cameras (shown in Figure 8.1B) were placed around the participant (one on each upper corner of the nulling coils, and one in front of the participant). The cameras were calibrated using the Motive Software; this procedure was able to compute the position and orientation of each camera and the amount of distortion in images to construct a 3D capture volume. This is achieved by using 2D images from each of the synchronised cameras and associating the position of known calibration markers (using a calibration wand supplied with the system) from each camera through triangulation (Figure 8.1C). In order to reconstruct an infrared marker, it must be seen by at least 3 cameras. By surrounding the participant with cameras, there is a greater chance of seeing the markers no matter what movements they undertake, something which was challenging using the single V120:Duo camera. This enabled us to place markers not only on the helmet to track head movements, but also on gloves worn by the participant so that left and right hand movement could be individually monitored to more accurately time the point of movement cessation, rather than using the paradigm timings alone (Figure 8.1D).

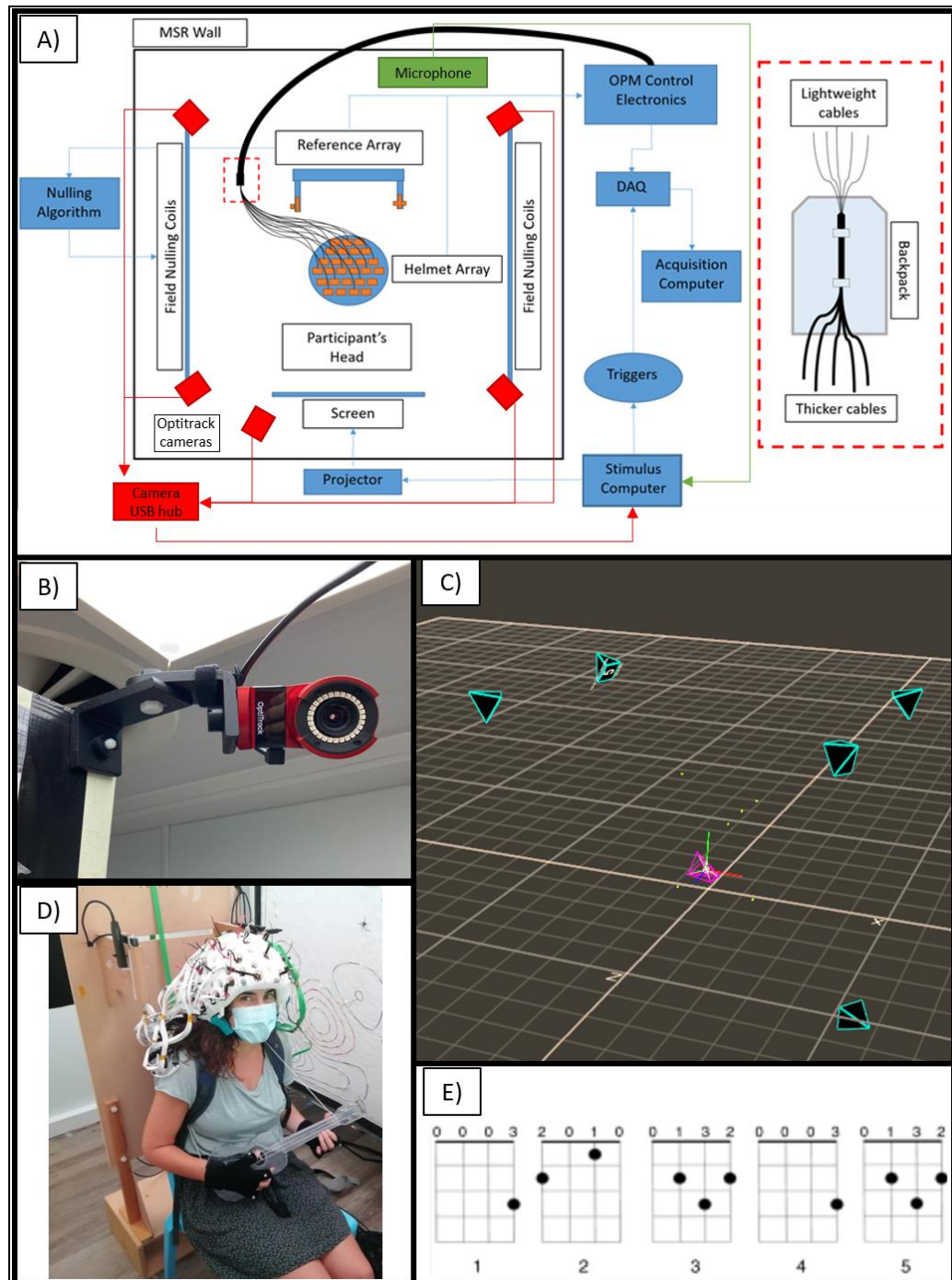


Figure 8.1: The OPM-MEG system. A) Schematic diagram of the whole system. Practically identical to the one shown in Chapter 7 aside from the new Optitrack setup (shown in red) and the microphone at the back of the room (shown in green). B) A Flex-13 camera mounted on the upper corner of the bi-planar coils. C) 3D capture volume after the cameras have been calibrated together. Markers placed on the coil to the left of the participant can be seen in green, and a rigid body formed by the helmet markers can be seen in pink. D) Participant setup. Note the gloves with small IR reflective markers to identify left and right hands. E) Visual prompt shown to participants.

8.2.2 Paradigm design

The paradigm was identical to that described in Chapter 5.2.3. The participants were asked to learn to play a sequence of five chords (C, F, G, C, G) on a ukulele (shown in Figure 8.1D). The chords were visually projected onto a screen (shown in Figure 8.1E), and the participants were given 5 s to complete the sequence, with a 10 second rest after each attempt. On the prompt to rest, the participants were asked to release the ukulele (which was suspended around their neck) and place their hands on their lap. Once again, we expected to see the beta desync/rebound pattern seen in Chapter 4.6. This was repeated 40 times each day, with a total of 200 trials performed over the 5 days.

8.2.3 Data acquisition

46 OPMs were available for these experiments and were placed across the 50 slots in the rigid helmet used in Chapter 7, with the most anterior slots being sacrificed (see Figure 8.2).

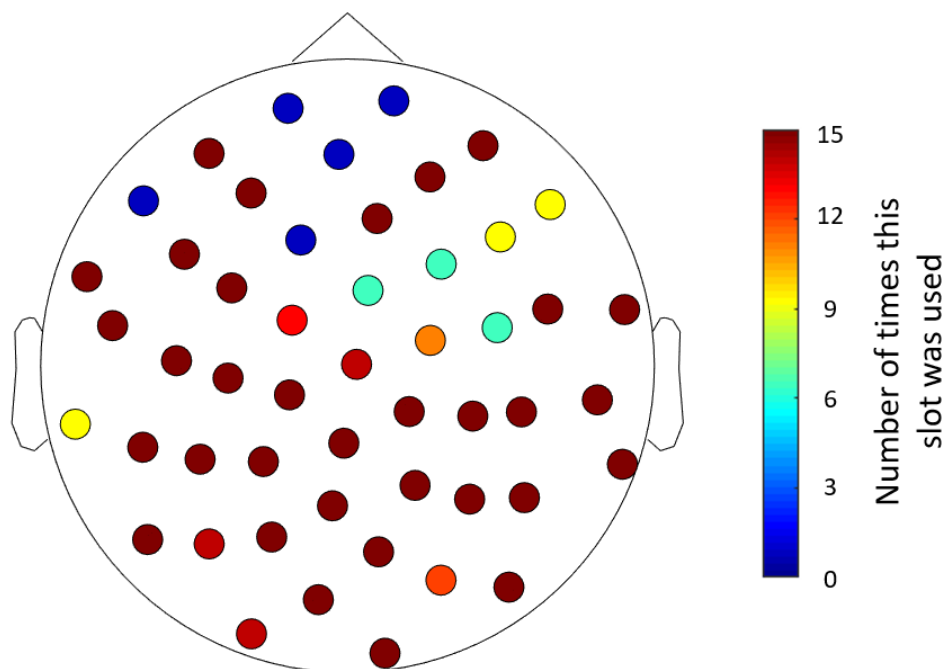


Figure 8.2: Near whole-head coverage. The 50 slots in the rigid helmet represented as a flat map. The colour of the dots for each slot represents how many times that slot had usable data (15 in red, 0 in blue).

Audio was recorded by a MATLAB program (sampled at 8000 Hz) which also controlled the paradigm, as well as the Motive software (for recording the Optitrack data, sampled at 120 Hz) using the NatNet SDK software described in Chapters 4 and 5. The audio and Optitrack recordings were started and stopped simultaneously, with a temporal marker being sent to the DAQ to allow the OPM data to be synchronised to the audio and motion tracking recordings.

8.2.4 Data analysis

We first bandpass-filtered all data between 1 and 150 Hz, and removed any 'bad' trials (specifically, trials in which the standard deviation of the signal at any one sensor was greater than 3 times the average standard deviation across all trials were removed). We also visually inspected the data and removed any 'bad' channels where excessive interference dominated the signal. Across all 15 runs, 6 had the total sensor count reduced to 42 'good' channels, 8 runs reduced to 41, and 1 run reduced to 38. Most of these cases were due to sensors being unable to start. In such an instance, these sensors were swapped with sensors at the front of the head to ensure that we always had good coverage of the sensorimotor cortex. Some cases were due to an unusual source of noise being detected on the sensor which propagated through the chain of modulation cables that connect the OPM electronics modules together. Once again, these sensors were swapped to the front of the helmet to keep coverage over the sensorimotor cortex, but if the abnormal noise was still present just prior to recording, the sensors were turned off. The remaining bad channel cases were if a sensor turned off during the scan, either due to overheating or because of an issue with the laser locking. Unfortunately nothing could be done if these occurred over the sensorimotor cortex. Figure 8.2 shows how many times each slot had usable data (out of a possible 15). The sensorimotor cortex is typically very well covered (as demonstrated by the colour scale in Figure 8.2).

Co-registration was performed immediately after data collection using the method for the rigid helmet described in Chapter 6. For all participants, the anatomical MRI was acquired using a 3T MRI scanner running an MPRAGE (Brant-Zawadzki, 1992) sequence, at an isotropic spatial resolution of 1 mm. A beamformer technique (Robinson and Vrba, 1998) as described in Chapter 2.2 was then used to localise sources of beta modulation. The regularisation parameter was set to 0.05 times the maximum eigenvalue of the un-regularised matrix, and the active and control covariance windows were taken at $1\text{ s} < t < 3\text{ s}$ and $5\text{ s} < t < 7\text{ s}$ relative to movement cessation respectively. This contrasts the beta-rebound period to the rest period. We use movement cessation as each trial is of varying length depending on when the participant stopped playing the ukulele.

8.2.5 Audio analysis

In order to assess how the neuronal response changes depending on the participant's performance, we required a method for scoring the trials. There are many ways we can consider scoring a person's playing: the speed at which they play; the clarity of the chords; the number of chords they manage to achieve; manually listening to every trial and scoring it; etc. However, as a relatively simple and automated way to assess the participant's performance, we performed a frequency analysis on the recorded audio.

As the ukulele is a four stringed instrument, there are four possible notes in any one chord. Without going into too much music theory, a standard chord is the combination of only three notes (e.g. a C chord contains the notes C, E, and G). Each of these notes has their own frequency, and the frequencies in each chord are shown in Table 8.1. The subscript number denotes the

octave¹⁴ in which the note is located when played on a ukulele in standard tuning.

Chord	Note 1 Frequency (Hz)	Note 2 Frequency (Hz)	Note 3 Frequency (Hz)	Note 4 Frequency (Hz)
C	G ₄ = 392	C ₄ = 261.63	E ₄ = 329.63	C ₅ = 523.25
F	A ₄ = 440	C ₄ = 261.63	F ₄ = 349.23	A ₄ = 440
G	G ₄ = 392	D ₄ = 293.66	G ₄ = 392	B ₄ = 493.88

Table 8.1: Chord composition. The notes and the corresponding frequencies that make up each chord used in this paradigm.

In each chord we see that at least one note is repeated, either at the same pitch or higher. This is because there are only three notes in the chord, but there are four strings on the ukulele. Figure 8.3 shows the fingering for each chord, and the notes they correspond to below to better demonstrate why certain notes are repeated.

¹⁴ An octave is the interval between one musical pitch and another with double its frequency. These will be the same note as each other but at different pitches. For example, for A₄ = 440 Hz, one octave down (i.e. the same note at a lower pitch) is A₃ = 220 Hz, and one octave up (the same note at a higher pitch) is A₅ = 880 Hz.

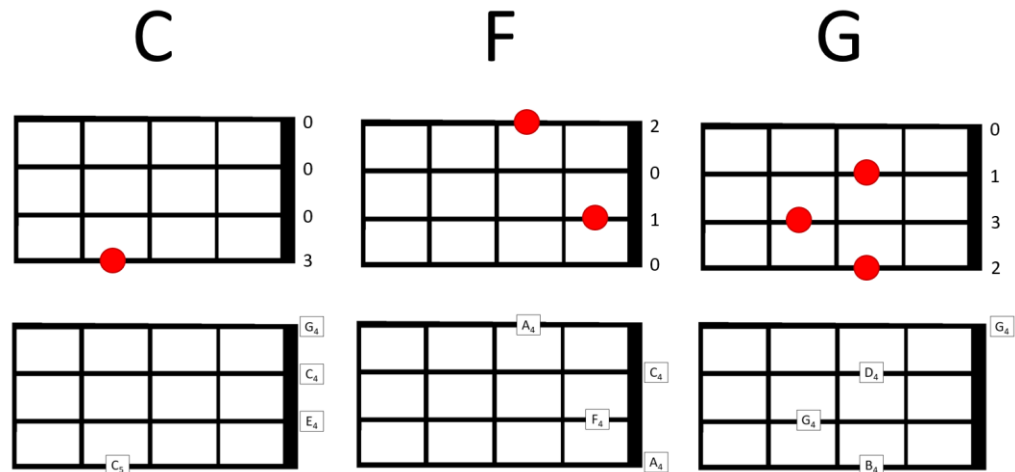


Figure 8.3: Chord composition on the ukulele. The red dots show the finger placement on the ukulele fretboard, with the numbers to the right representing which finger is used (0 = no finger, 1 = index, 2 = middle, 3 = ring). Below, the same diagram can be seen with the fingering replaced by the corresponding notes. The fretboard is set out as if you are facing a right handed player playing the ukulele (i.e. frets go from highest on the left to lowest on the right).

Frequency analysis on the recorded audio allowed us to find which of these frequencies were present. First, we split the audio into trials, then identified when the chords are played by finding the peaks of the audio waveform (see Figure 8.4A). For each chord, we performed frequency analysis over a 0.6 s window¹⁵ (0.3 s either side of the peak), and identified the notes that were present. Because the ukulele is plastic, its intonation (how in tune the notes are as you move further up the fretboard) and its tuning stability (how long the strings remain in tune) are poor, and so the notes will not be precisely the correct frequency, instead they may be slightly sharp (higher frequency) or slightly flat (lower frequency) (which was accounted for by finding the closest corresponding note within 15 Hz).

¹⁵ If a person played all 5 chords in 5 seconds, it would be one chord a second, but time would need to be allowed for to change chords. The 0.6 s window allows enough time for all the strings to be strummed without picking up additional noise from changing chords.

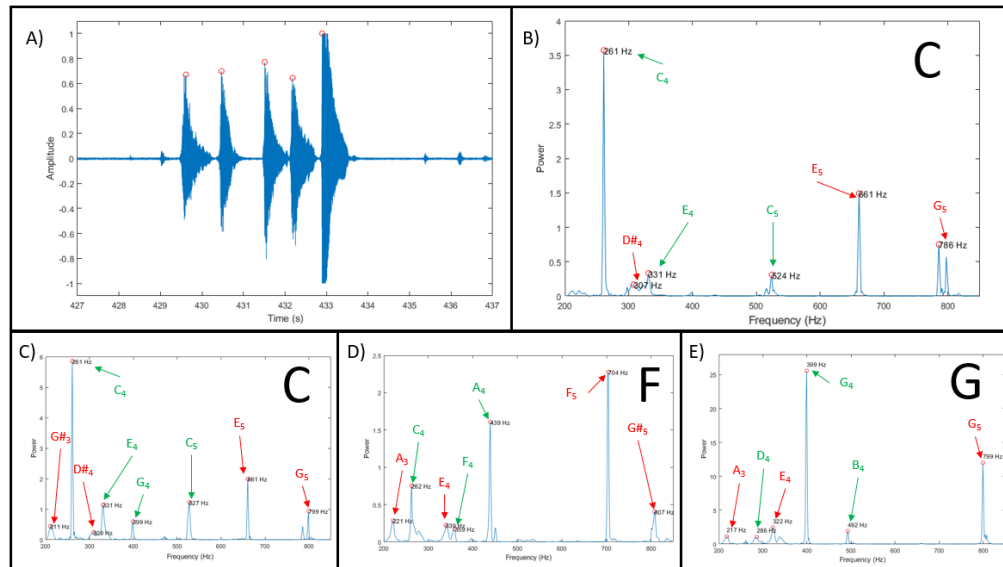


Figure 8.4: Chord detection and analysis. A) Waveform from the recorded audio during a single trial in which a participant managed to play all 5 chords. B) Fourier analysis of the first peak in A which should be a C chord, but is missing the G_4 note. Green labels and arrows indicate correct frequencies, and red indicates other frequencies. C-E) Fourier analysis of a correctly played C, F and G chord (taken from the 4th, 2nd, and 5th peak in A respectively).

Because the paradigm requires that the participant plays the chords in order, regardless of whether they played it correctly or not, we can check whether the frequencies associated with each chord are detected in turn. For example, Figure 8.4A shows the waveform of a trial in which 5 chords are played. Figure 8.4B shows the Fourier spectrum for the first detected chord (C). The correct frequencies are shown in green, and any other frequencies shown in red. This chord is not wholly correct as it is missing the G_4 note and, while the G_5 note is present, this would not count as having all three required notes for the C chord (C , E , and G). This is because the G_5 is present due to semi-muting the string when playing G_4 (most likely due to other fingers being in the way) which causes the string to ring as a “pinched harmonic”¹⁶. In Figure 8.4C we see another spectrum for the C chord but this time where all the expected frequencies are present. Note that the G_5 is present here as well but this is as

¹⁶ This is actually a technique that can be employed on purpose in guitar to give those awesome squeals during a solo, but they are also the result of a poorly played chord when done by accident.

a natural harmonic of the note played. Figure 8.4D and E show correctly played F and G chords for reference.

The additional frequencies are mostly caused by harmonics in the instrument, but they can also be due to accidentally hitting other strings, or the microphone picking up other sounds such as any noises from outside of the MSR (e.g. talking or a delivery truck beeping while it reverses). However, these additional frequencies make it difficult to simply analyse waveform to work out what chord was being played and score it (though not impossible). Instead we kept the scoring simple:

1. For each trial, detect the first chord and find how many correct notes from the first chord in the sequence (C) are played. This would give a **chord score** out of 4. For example, Figure 8.4B would score 3/4.
2. Repeat step 1 for the rest of the chords (i.e. compare the 2nd detected chord with the 2nd chord in the sequence, F, and so on), and sum the individual chord scores for each trial to get a **trial score**. There are 5 chords per trial so this would be scored out of a possible 20. If, for example, only two chords were played during a trial, the remainder of the chords would be scored as 0, so even if those two chords scored 4/4 each, the trial score would be 8/20.
3. Repeat this for all trials to get a distribution of trial scores.

While simple, this technique prevents any ill-timed external noise from negatively affecting the scores, and provides a relatively quick and robust method of scoring the participant without having to manually listen to 200 chords per participant.

8.2.6 Motion analysis

The nature of this paradigm forces the participants to look away from the projection screen and down at the ukulele as they try to play the chords.

This means that they often do not immediately see that the 5 seconds are up, and continue to play for a few seconds after the paradigm instructed them to stop. Even if they do see the “finish” prompt, it takes a second to release the ukulele and rest their hands. This makes it difficult to truly know when movement has stopped, and the experimental timings can be thrown off. In order to solve this, we used the Flex-13 Optitrack system to track hand movements, allowing us to accurately time the onset and offset of motion in post-processing.

The markers placed on the participant’s hands (as shown in Figure 8.1D) were continuously tracked throughout the experiment. The origin of the 3D capture volume was set to the participant’s chair, with the positive x-axis defined in the direction they are facing (i.e. towards the projector screen) and the positive z-axis defined towards the bi-planar coil to the right of the participant. This allows the two hands to be distinguished by simply looking for markers either side of the origin in the z-axis (i.e. the left hand will have negative z coordinates, and the right hand will have positive) as shown in Figure 8.5A and B.

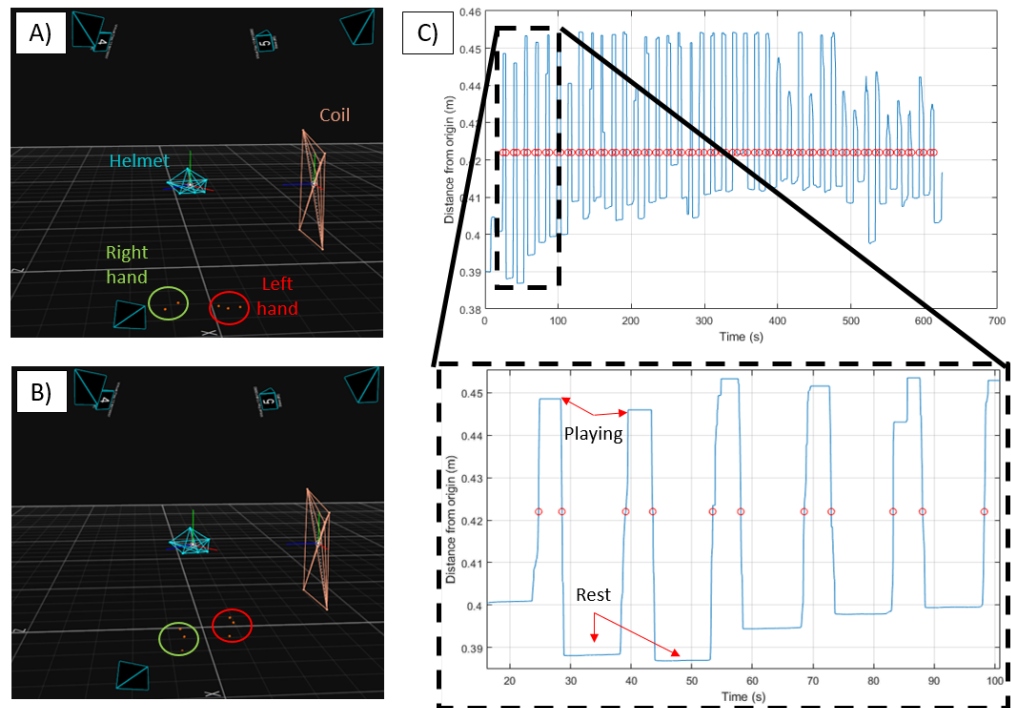


Figure 8.5: Motion tracking data. A) The 3D capture volume while the participant is resting their hands on their lap. B) The same capture window as the participant plays the ukulele. In both images, the left and right hand can be easily distinguished by their position along the z-axis. The blue shows the helmet rigid body, and the orange shows the bi-planar coil to the left of the participant as a point of reference. C) The upper plot shows the how the left hand changes its distance from the capture volume origin over time. The lower plot is a zoomed in portion of the same plot. Red circles show the detected movement onset and offset, and are placed at a threshold value that separates the hand on the lap during rest to the hand on the ukulele while playing.

Because the hand can bend and change shape, we were not able to create a rigid body from the markers placed on each hand. It could be possible to add some sort of rigid plate to the back of the hand to keep the markers in a fixed separation from each other, but this would affect hand mobility and could become uncomfortable for the participant, especially when they are already having to make movements they aren't used to when playing the ukulele. Instead, we created a “pseudo” rigid body by finding the mean of the markers associated with each hand. As we are only interested in the movement of the hand to and from the ukulele (not necessarily the rotation), the average point for each hand gives us enough information. However, in future versions of this task, it may be necessary to create actual rigid bodies to gain more information, or use skeletal tracking.

The onset and offset of movement for each pseudo rigid body was found by first distinguishing between when the hands were at rest on the lap and when the hands were on the ukulele. We found the distance from the origin for each time point, and set a threshold value (shown by the height of the red circles in Figure 8.5 C) that distinguished between the hands being on the lap during rest and playing the ukulele. Anything above the threshold was set to 1, and anything below set to 0. By calculating the difference between adjacent elements of this “binary” trace, we can search for values of +1 and -1 to determine movement onset and offset respectively. Because the left hand performed the more difficult movements (making the chord shapes) and is notionally of more interest in a motor learning capacity, we used the left hand triggers in the data analysis.

8.2.7 Left vs. right hemisphere peak location

When playing the ukulele, the left hand action involves bending the fingers to make chord shapes, while the right hand strums the ukulele, an action which typically uses more of the wrist and forearm. If we look at the cortical homunculus diagram (Figure 8.6), we can see that cortical representations of the wrist and arm responses are slightly superior in the brain compared to those of the hand. We may therefore expect to see differences between the peak locations in the left and right hemisphere for beta activity, assuming that the beta response maps motortopically (Barratt et al., 2018).

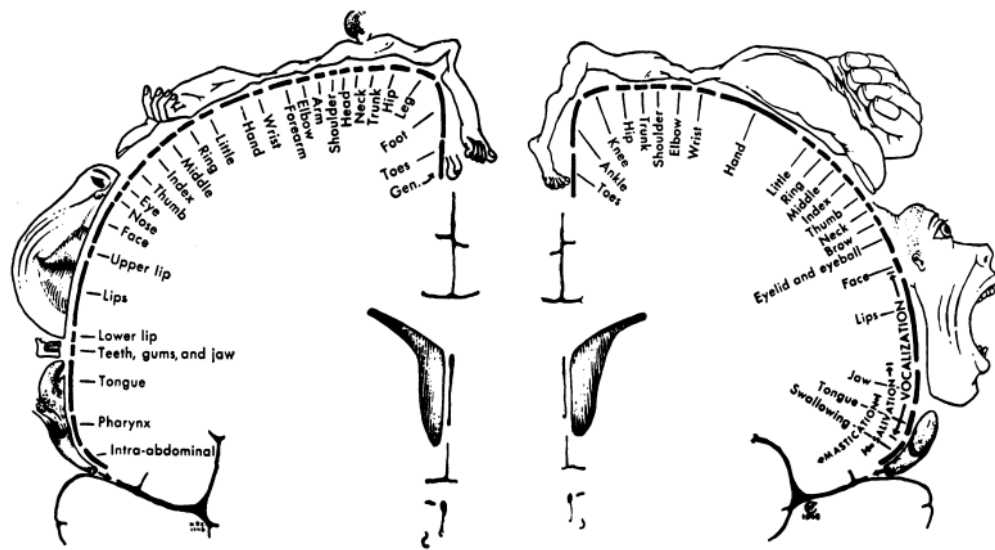


Figure 8.6: The motor and sensory homunculus. Adapted from Penfield and Rasmussen (Penfield and Rasmussen, 1950).

In order to test this quantitatively, we assumed that the left hemisphere of the brain is a mirror image of the right, and found the location of maximum beta rebound in each hemisphere. We then compared the z-coordinate (i.e. the superior-inferior measurement) of each peak voxel. We reasoned that the peak in the left hemisphere (i.e. the right hand) should be have a larger z-coordinate than the right. Because the beamformer was performed using 4-mm voxels, a difference of 1 voxel corresponds to a distance of 4 mm

8.2.8 Beta rebound amplitude vs. trial score

We investigated the relationship between beta rebound amplitude and trial score using a virtual electrode in the peak voxel from the right hemisphere (i.e. relating to the left hand). For each participant, the virtual electrodes from each of the 5 datasets were concatenated, resulting in a virtual channel with 200 trials which was then filtered to 13 – 30 Hz. For each trial, the mean Hilbert transform amplitude was found during the ‘On’ window ($-2 \text{ s} < t < -0.5 \text{ s}$ relative to movement cessation) and the ‘Off’ window ($0.5 \text{ s} < t < 2 \text{ s}$ for Subject 1, and $1.5 \text{ s} < t < 3 \text{ s}$ for Subjects 2 and 3), as well as the difference between these amplitudes. The individual trials were paired with the trial scores (from section

8.2.5) and separated into lower, middle, and upper 33% percentile groups (based on the individual participant's score distribution). The mean amplitudes and the standard deviation for the low and high scoring trials were then found.

We expected to see the beta rebound amplitude higher with better performing trials. Briefly, beta oscillations are thought to exert top-down influence on the cortex. A predictive coding model would suggest that, in the post-movement window, this influence would be greater following correctly played trials than incorrectly played trials.

8.2.9 Functional connectivity

Functional connectivity is defined as a statistical relationship between neuroimaging signals derived from spatially separate brain regions. When one or more occurrences of functional connectivity exist between regions, we say those regions form a network. In order to assess the networks, we first reconstructed the neuroimaging signals in different regions of the brain.

We divided the brain into 78 discrete cortical regions defined by the Automated Anatomical Labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). A scalar beamformer was used to obtain a single virtual electrode placed at the centre of mass of each cortical region (creating 78 virtual electrodes in total). The data covariance matrix was computed in the 8 – 80 Hz frequency range across the whole experiment. The regularisation parameter was set to 0.05 times the maximum eigenvalue of the un-regularised matrix, and the forward model was based on a single sphere model. Following this, the 78 virtual electrodes were each frequency-filtered to the beta band (13 – 30 Hz), and epoched into trials. Signal leakage between the regions was corrected using

pairwise orthogonalisation¹⁷ (Brookes et al., 2012; Hipp et al., 2012). The amplitude envelope of the oscillatory signals was calculated using the absolute value of the Hilbert transform of the frequency filtered data, and was then down-sampled to 10 Hz. The Pearson correlation between all possible AAL region pairs was calculated, resulting in a 78 x 78 adjacency matrix representing whole brain activity for each trial.

The connectivity was assessed in two ways. We first looked at how the connectivity changed across each day. Second we paired the trials with the trial scores, and averaged across low and high scoring trials. We then found the differences between the high and low scoring adjacency matrices. Connectivity strength (the summed connectivity between each region and all other regions) for each matrix was found by summing the matrix in one dimension, resulting in a 78 x 1 vector.

8.3 Results

8.3.1 Source localisation and reconstruction

Figure 8.7 shows the average T-statistical image for all 5 runs for each participant, as well as the average reconstructed timecourse in the beta band for the peak voxel in the right hemisphere. All three participants show peak beta modulation in the right sensorimotor cortex (i.e. the region responsible for the left hand movement). Subject 1 also shows a large beta modulation in the left sensorimotor cortex, as do Subjects 2 and 3, but at a lower amplitude that is masked by the thresholding applied in Figure 8.7 (this is addressed below). The average reconstructed timecourse for each participant also shows

¹⁷ We did not use symmetric orthogonalisation as there are fewer sensors than seed locations. It is impossible to make 78 orthogonal signals from 50 signals, whereas for pairwise orthogonalisation, only 2 signals must be made independent before measuring the connectivity.

the characteristic beta desynchronisation during movement, followed by the beta rebound above baseline on movement cessation. The maximum range of head movement performed by the three participants was 15.8 cm and 46.3° (mean of 7.2 ± 3.5 cm and $19.7^\circ \pm 10.8^\circ$ across trials).

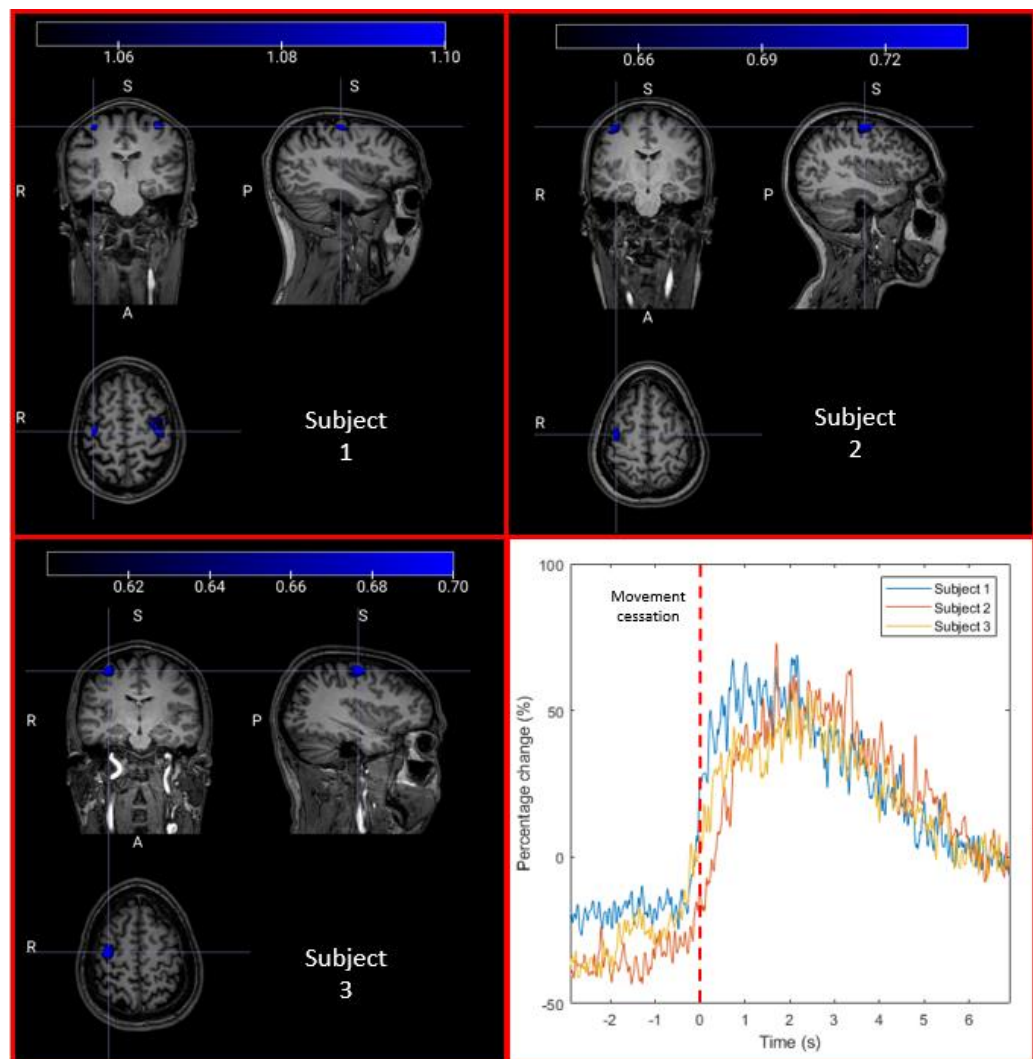


Figure 8.7: Source localisation and reconstruction. The spatial signature of peak beta modulation during the beta rebound period following movement cessation ($1\text{ s} < t < 3\text{ s}$) for each participant, averaged across all datasets (note that left and right are swapped i.e. in radiological view). The average reconstructed time course for the peak location in the right hemisphere is shown in the bottom right, with a red dashed line denoting movement cessation at $t = 0\text{ s}$.

Figure 8.8 shows the repeatability of the source reconstruction for each participant. For each participant, the reconstructed timecourse for each day is overlaid in the left-most plot. The next plot shows the average of all 5 time courses and the standard deviation in the shaded area behind. The brain plots

show ellipsoids like those presented in Chapter 7.5.2 to show how the peak location varies for each hemisphere across the 5 runs for each participant. The centre of each ellipsoid represents the mean location of the peak in the relevant pseudo-T-statistical images for beta modulation. The size of the ellipsoids represents the standard deviation of the peak locations (measured independently in three orthogonal axes). All three participants show very reliable repeat measurements, and the ellipsoids are small and well localised to the left and right motor cortices. This strongly supports our first hypothesis that our whole-head system is as motion robust as our previous systems.

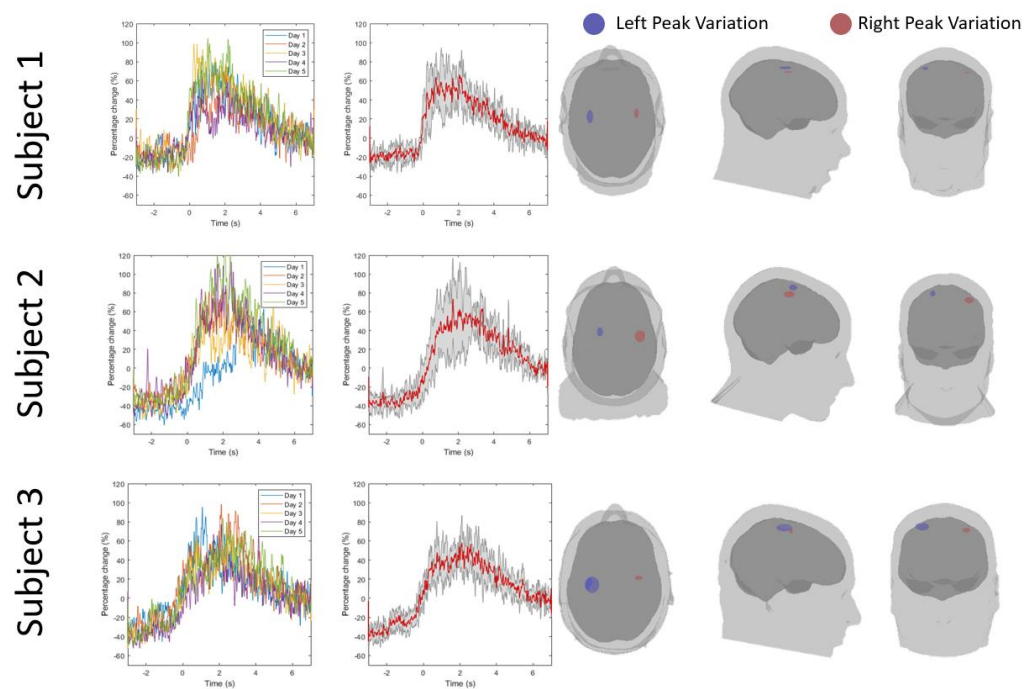


Figure 8.8: Repeatability. The repeatability of the reconstructed sources and time courses. For each participant, the left-most plot shows the reconstructed beta modulation trace for each day overlaid. The next plot shows the average trace for all 5 days and the standard deviation in the shaded region behind it. The MRI plots show a glass brain with the centre of the ellipsoids showing average peak location in the left and right hemisphere across runs. The size of the ellipsoids represents the standard deviation of the peak locations.

8.3.2 Left vs. right hemisphere peak location

Figure 8.9 shows the average T-statistical image for all 5 runs with the threshold altered to show the peak activity in both hemispheres, and the z value of the peak voxel for beta activity in each hemisphere. Subjects 1 and 2

continuously show activation at a location superior in the cortex in the left hemisphere compared to the right on every day. The average T-stat image for Subject 2 also clearly shows the asymmetry between the two hemispheres. For Subject 3, three of the five datasets show the expected asymmetry, but one of the days shows the z-values as being equal, and the other with the opposite asymmetry to that expected. This demonstrates a systematic shift in location which is likely because of the left fingers being used for forming the chords, and the right wrist/forearm for strumming. These results support that the spatial resolution achieved by this system is enough to see left/right hemisphere asymmetry.

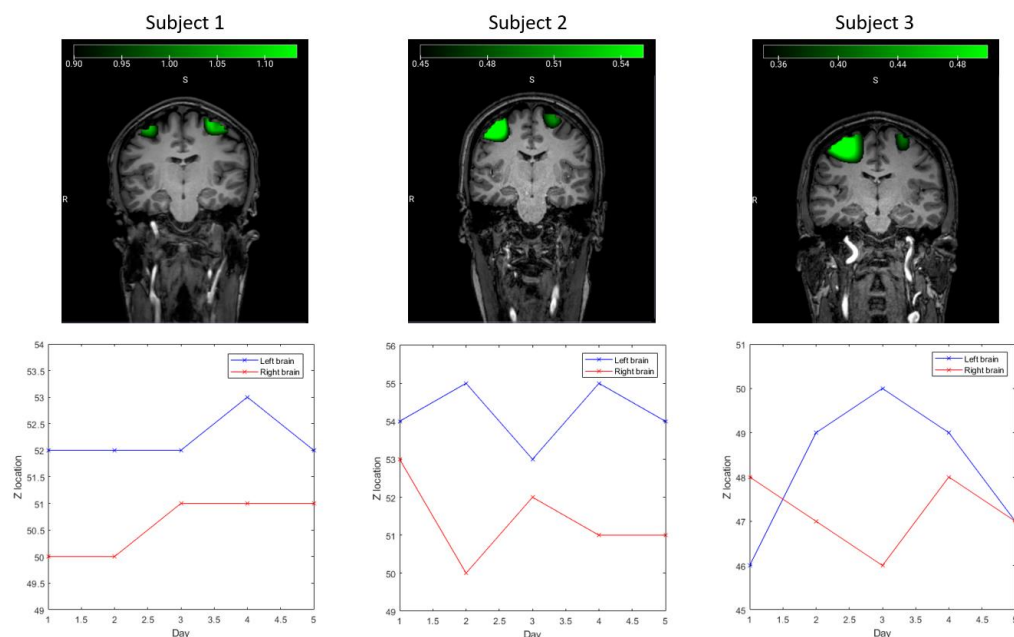


Figure 8.9: Peak locations in each hemisphere. The top row shows the average T-stat image for all 5 runs with the threshold altered to show the peak activity in both hemispheres (note that it is once again shown in radiological view). The bottom row shows the peak voxel z-value for both hemispheres in each dataset. The left hemisphere is shown in blue, and the right hemisphere shown in red.

8.3.3 Beta rebound amplitude vs. trial score

Figure 8.10 shows the score distributions for each participant, as well as the beta amplitude for the “On” (beta desynchronisation period) and “Off” (beta rebound period) windows and their difference for the low and high scoring groups. All three participants show an increase in the On-Off difference

with higher trial scores, though Subject 3 is less pronounced. By performing a Wilcoxon rank sum test on these differences for each participant, we obtain p-values of 3.5×10^{-3} , 1.5×10^{-6} , and 0.13 respectively (therefore the results are significant for Subjects 1 and 2). This result therefore supports (at least in part) our hypothesis that beta modulation would change systematically according to success in the task.

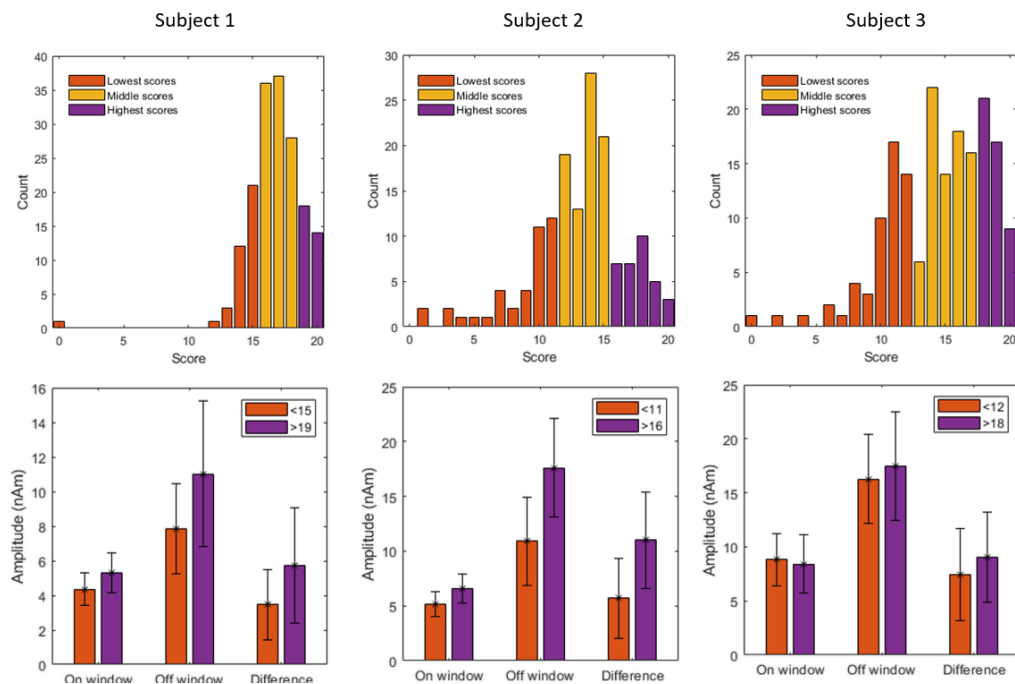


Figure 8.10: Beta amplitude vs. score. The top row shows the score distributions for each participant with the lowest scoring trials in orange, the middle scoring in yellow, and the highest scoring in purple. The bottom row shows the average beta amplitude in the “On” and “Off” regions and the standard deviation as well as the difference between the two regions for the lowest and highest score groups (with scores shown in the same colours). Note, the high and low scoring groups are the upper and lower thirds respectively. The middle third is excluded.

8.3.4 Functional connectivity

Figure 8.11 shows the connectivity results for each dataset. The connectivity matrix for beta band activity is shown on top, and the two brain plots below show the connectivity strength (i.e. the correlation of each region to all other regions) on the left, and the correlation of the right motor cortex with all other regions on the right. The diagonal of the matrix (i.e. the correlation of a region with itself) is set to 0 for simplicity. Consistent

connectivity structure can be seen in all datasets apart from Day 4 for Subject 3 where frontal regions seem to dominate. Otherwise, the right motor region typically shows a strong connection to the left motor region.

Figure 8.12 shows the connectivity strength averaged across all five datasets for each participant. The standard deviation across these runs is shown in the shaded regions behind each line. All three participants show very similar plots, and the highest peaks correspond to sensorimotor areas, as expected given the nature of the task. The amplitude of the strength differs across the participants and is consistently higher for Subject 3 across all regions.

Figure 8.13 shows the connectivity for the low and high scoring trials for each participant, as well the difference between them (high scoring trials minus low scoring trials). Once again, the connectivity matrix is shown on the left and the connectivity strength is shown on the brain plot to the right. Clear structure can be seen in all participants but no coherent effect can be seen in the differences between high and low scoring trials.

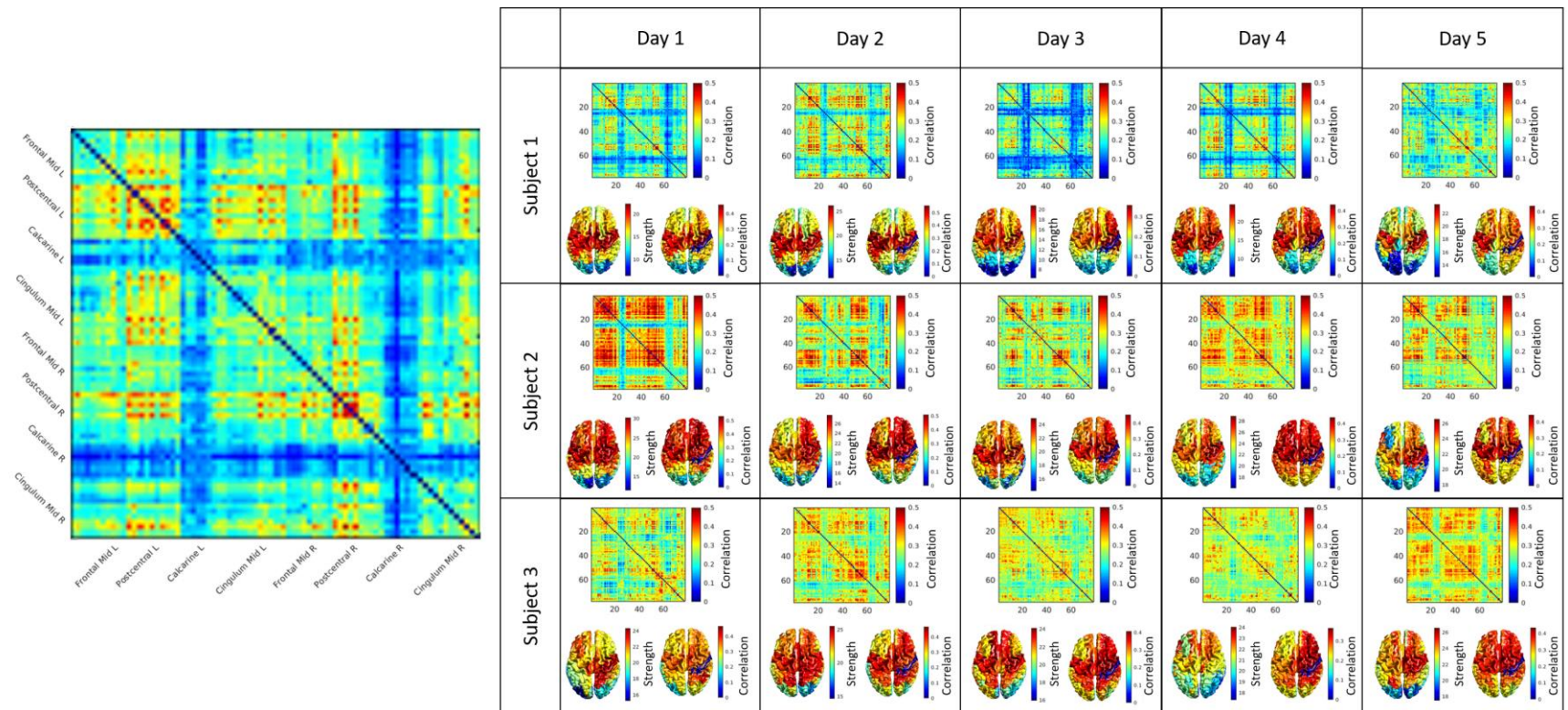


Figure 8.11: Functional connectivity per day. The changes in functional connectivity for each participant for each dataset. In each dataset, the Amplitude Envelope Correlation (AEC) matrix is shown on top, with red colours representing strong correlation and blue representing weaker correlations. Below, there are two brain plots. The left brain shows the connectivity strength (i.e. the correlation of each brain region to all other brain regions), while the right brain shows the correlation of only the right motor cortex to all other regions. Note, the diagonal of the matrix (i.e. the correlation of a region with itself) is set to zero for simplicity. The single plot on the left is from Subject 1, Day 1 and is there to identify the sections of the connectivity matrix.

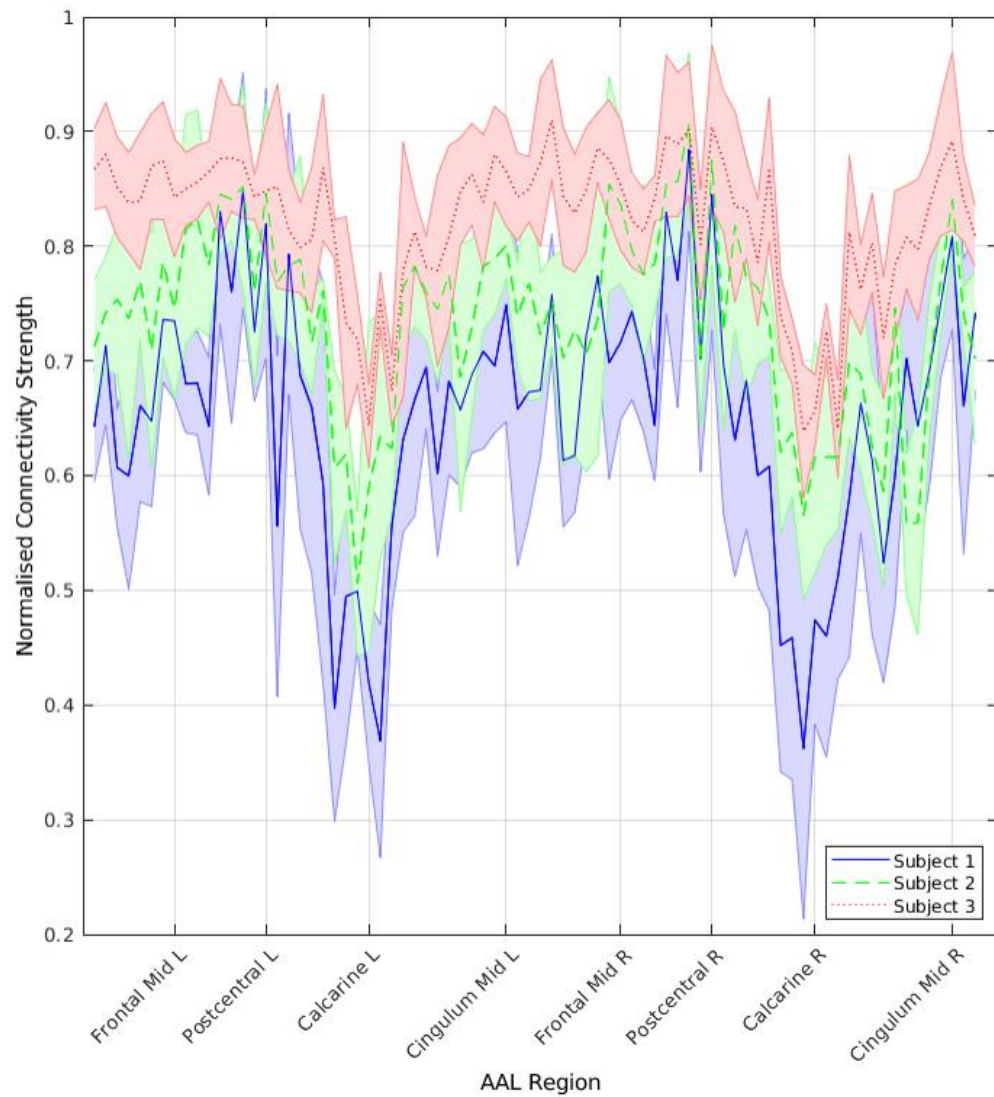


Figure 8.12: Normalised connectivity strength. Values are plotted for all 78 regions for all three participants (Subject 1 solid blue line, Subject 2 dashed green line, and Subject 3 dotted red line). The shaded area represents the standard deviation across the five runs for each participant.

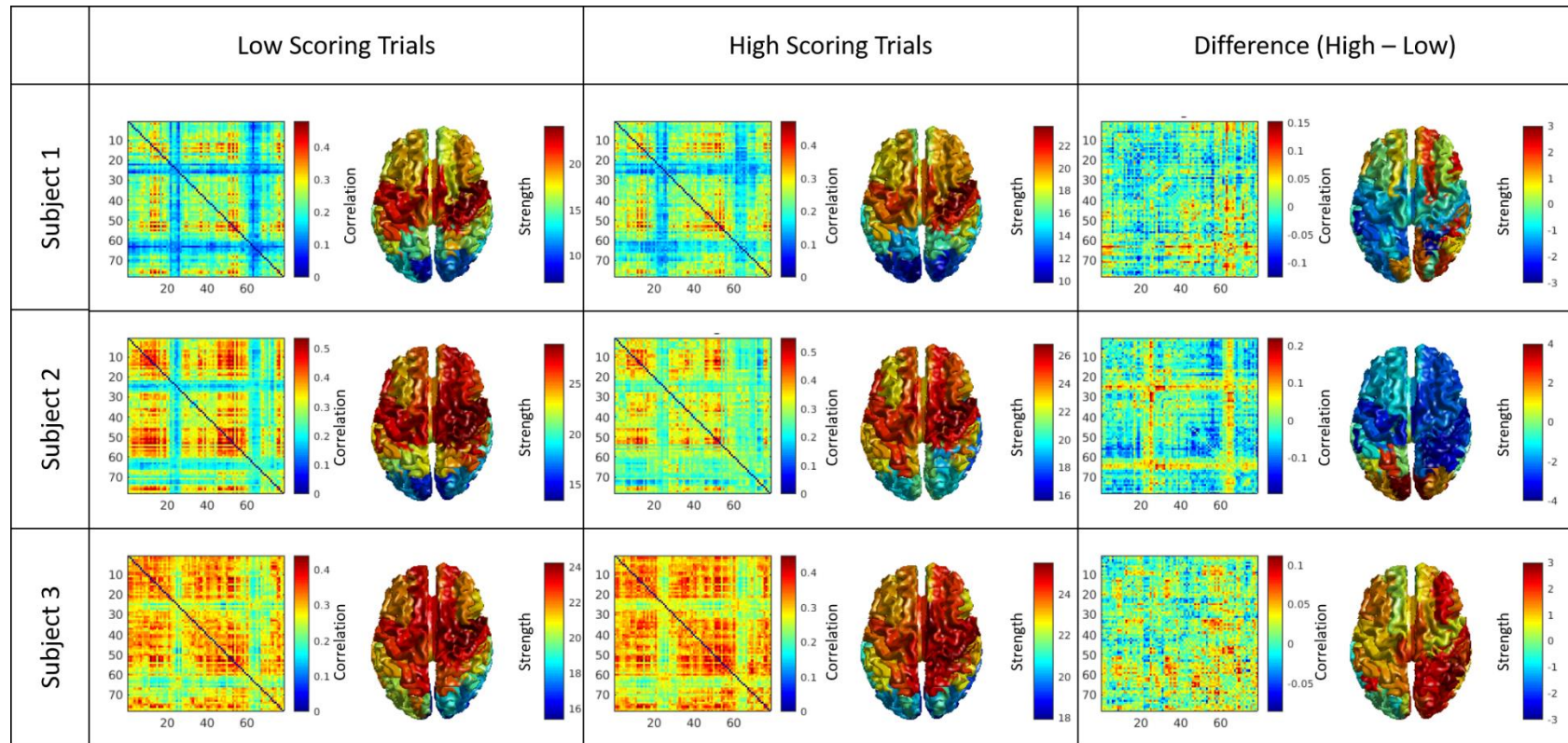


Figure 8.13: Functional connectivity per score. The functional connectivity for the low scoring and high scoring trials for each participant, and the difference between them (High minus Low). For each condition, the AEC matrix is shown on the left and the connectivity strength is plotted on the brain.

8.4 Discussion

In this chapter, we have combined the system developed in Chapter 6 and 7 with the novel motor learning paradigm presented in Chapter 5. We devised a scoring system in order to rate the participant's performance in each trial, and used a new motion tracking system to accurately determine the onset and offset of motion to obtain accurate paradigm timings. This has enabled us to acquire high fidelity pilot data while performing a novel paradigm, which will eventually allow us to probe the brain function involved in motor learning.

8.4.1 Technical discussion

We have once again seen high fidelity data acquired using our generic 50-channel OPM-MEG system even when performing naturalistic movements. Using the Optitrack cameras, these head movements were found to have a maximum range of 15.8 cm and 46.3°¹⁸. Despite these large movements, all datasets were able to be source localised to the motor cortex, and have their timecourses reconstructed. The expected beta modulation was repeatedly observed in every dataset, and the peak localisation error represented by the ellipsoids in Figure 8.8 all occur in the expected regions of the brain.

More than that, the left and right hemispheres were localised to different regions of the motor cortex, with the right hemisphere (responsible for the left fretting hand) localising more inferior in the motor cortex than the left hemisphere (responsible for the strumming motion in the arm/wrist). This is, however, a simplified method for showing asymmetry in the brain and it assumes that both hemispheres of the brain are completely symmetric.

¹⁸ Max translations and rotations for each participant:

Subject 1: 7.56 cm and 27.5°

Subject 2: 14.0 cm and 42.3°

Subject 3: 15.8 cm and 46.3°

Nevertheless, it is still promising that we can attempt to make such a distinction even with a relatively low sensor count compared to SQUID-based systems and the large range of motion by the participant. This supports our first hypothesis that our 50-channel whole-head system is as motion robust as the system shown in Chapters 4 and 5. This is not a trivial achievement as the artefacts produced by cable interactions (discussed in Chapter 6, Section 7) are likely to be amplified when a participant performs large movements. In our previous demonstrations, the steps taken to ameliorate these problems were tested in the context of a paradigm that does not require the participant to make large naturalistic movements, and so it was unknown whether the measures would still be sufficient. The use of the back pack to secure the sensor cables to the participant, and the securing of the flex cables to the helmet prevented the large participant movements from pulling on the sensor's internal components. The taping of the cables to prevent cable crosstalk was also sufficient despite the movement, which is largely thanks to identifying and controlling the effect in the worst-case scenario (in Chapter 6, Section 7.2). Overall this allowed for data that were sufficiently high fidelity to detect small modulations of signal amplitude due to task performance.

We also explored functional connectivity while performing the ukulele task. Boto et al. (Boto et al., 2020) has shown that both task-based and resting state connectivity can be investigated using OPM-MEG with data fidelity similar to that of cryogenic systems, and robust differences between individuals scanned multiple times exist. However, Boto et al. did not attempt to measure brain activity during movement. Here we see regular connectivity structure in all datasets aside from one. We also see a similar pattern across all participants in the average connectivity strength for each region. These data suggest that connectivity structure remains visible, even in the case of high degrees of movement.

8.4.2 Neuroscience discussion

Firstly, from a neuroscientific point of view, we must stress that these are pilot data. We have only scanned a small number of individuals and the novel paradigm, coupled with the novel equipment, mean that our hypotheses and findings must be considered speculative. Nevertheless, the data that we generated are broadly supportive of a hypothesis that task performance systematically modulates the beta modulation in sensorimotor cortex; specifically we found that for 2 out of 3 subjects, a significant increase in beta rebound was present in higher scoring, compared to lower scoring, trials. For the third participant, the same trend was noted albeit without reaching statistical significance. This finding was expected, and is broadly supportive of the idea that beta oscillations are involved in top down influence of primary cortices.

In general, the predictive coding model of brain activity suggests that the human brain continually generates and updates a “forward model” of the world around us. In a Bayesian sense, this means we have a set of statistical priors relating to what will happen to us (the forward model), and these priors are continually updated based on incoming sensory information. Some authors (e.g. Arnal and Giraud (Arnal and Giraud, 2012)) have argued that neural oscillations represent directly, the predictive coding model, with beta oscillations carrying top-down influence that “imposes” the forward model on primary cortices. Indeed there is some experimental evidence for this. For example, using a paradigm in which participants had to move a cursor across a screen using a joystick, but where the correspondence between the direction of movement of the joystick and the cursor differed between trials, Tan et al. (Tan et al., 2016) showed that greater uncertainty led to a diminished beta rebound. This led to a hypothesis (Cao and Hu, 2016) that the absence of a rebound facilitates update of the forward model. This is not dissimilar to the effects observed here. When playing the Ukulele, we make a chord pattern

with the left hand, and strum the instrument, with our forward model predicting the sound that we will hear. If the sound is not as we expected, incoming sensory information must update the forward model – consequently we expected a diminished rebound – which is what we tend to see.

Again we stress that this is speculative. Proper testing of this would rely on a larger subject cohort and a more rigorous statistical assessment. In addition, in the present study, no behavioural testing was carried out and it is likely that the learning aspect of this paradigm could be improved by optimising e.g. the number of trials, and the number of days over which the experiment is carried out. In addition, giving participants time to practice in between scans may have also lead to greater variation in the behavioural scores. Nevertheless despite these shortcomings, what is shown here beyond doubt is that OPM-MEG offers a means to investigate the predictive coding model of brain function in a way that no other imaging modality can. This is perhaps a good example of how, in the future, OPM-MEG technology can uniquely begin to tackle some of the biggest contemporary questions that are being asked in the neuroscientific field.

8.4.3 Issues and future requirements

In order to measure the effects of motor learning in music, participants are typically split into two groups (musicians and non-musicians) and group differences are explored (e.g. Paraskevopoulos (Paraskevopoulos et al., 2012)). Here we are instead looking at the changes in an individual's brain as their performance changes, which could allow us to track the electrophysiological changes directly. Our scoring system is a somewhat simple way of measuring a participant's performance, but proved to be effective at distinguishing well played trials from poorly played trials. A more in depth measure of performance could eventually include other factors, such as the time taken to play each chord, the clarity of the chord (how clearly each note can be heard,

rather than simply measuring whether the note is present), or even using the motion tracking cameras to determine how precisely and smoothly the fingers are moved. However, this is something which must be explored further and could benefit from a discussion with a professional musician on the key aspects which must be considered.

Another potential issue is our ukulele. As it is a somewhat unreliable instrument, it could very easily go out of tune and also has poor intonation. Though this was accounted for in the scoring analysis, it is hard to account for the participant's perception of out of tune notes, and there could be an effect due to the participant knowing they've played the chord correctly but hearing an incorrect note (this may have been the case for Subject 3). It is hard to find a way to correct for this in a way that can still be MEG compatible as almost all instruments will have metal components. It may be that a specialised instrument could be created that meets our requirements. Alternatively, there has recently been a marked improvement in MIDI string instruments, such as a Jamstik MIDI Guitar which looks and plays like a guitar but does not produce acoustic sound. Instead, these instruments offer a purely digital signal, so no tuning issues would occur and the audio content could be more easily and directly analysed. Once again, these instruments are not MEG compatible as standard¹⁹.

Finally, the motion tracking system. Our Optitrack system successfully monitored both the participant's head movement and their individual hand movement. This allowed for much more accurate timings of the onset and offset of movement, so that any timing issues due to the participant's reaction times or them simply not immediately noticing the trial had finished could be

¹⁹ In addition, one of the challenging parts of playing an instrument is managing the acoustic noise. It is not necessarily putting the fingers in the right place that is hard, but putting them there correctly, such that the desired sound is produced and no annoying twangs are heard!

ameliorated. However, it may be that the tracking of individual fingers offers a greater insight into both the participant's ability and the brain response we expect to see. There are several ways in which to strum the ukulele: you can brush across it by only moving your thumb; you can brush your thumb or fingers across the strings using your wrist; you can do the same but move your whole arm; or you can do any and every combination of the above! While this will likely not change the beta rebound amplitude in the right hemisphere, it would change the expected peak location for the left hemisphere. Such tracking is possible with the Optitrack Flex-13 cameras which can perform skeletal tracking of the entire body. However, to accurately track the hands, the cameras would need to be moved closer to the participant which could potentially cause interference in the sensors.

8.5 Conclusion

In conclusion, we have shown that our 50-channel whole-head OPM-MEG system can reliably and robustly detect electrophysiological activity while a participant plays the ukulele. We have acquired pilot data that explores the relationship between the participant's performance and the associated beta activity modulation, and finds a significant result in two of the three participants, as well as a similar trend in the third. We have also been able to perform task-related beta-band connectivity analysis even while the participant is performing large head movements. This work will form the basis for a further study on a much larger cohort, and will help identify the analyses that will best assess the underlying electrophysiology when learning to play an instrument.

Chapter 9: Concluding remarks

9.1: Overview

Prior to the start of this thesis, Boto et al. (Boto et al., 2018) had demonstrated proof-of-principle of a wearable OPM-MEG system that allowed high fidelity data to be captured in free moving participants. However, this system, while offering great potential, had several limitations that prevented it from superseding the current state-of-the-art cryogenic systems. The work in this thesis has furthered this prototype to a viable commercial system that can directly compete with cryogenic MEG. Moreover, it demonstrates an adaptability to any head size or shape, as well as robustness to large motion made by the participant. This will allow full lifespan compliance by being able to scan young children who are prone to moving and fidgeting during scans, all the way through to older populations that may suffer from conditions such as tremor dominant Parkinson's Disease, which physically prevents them from staying still.

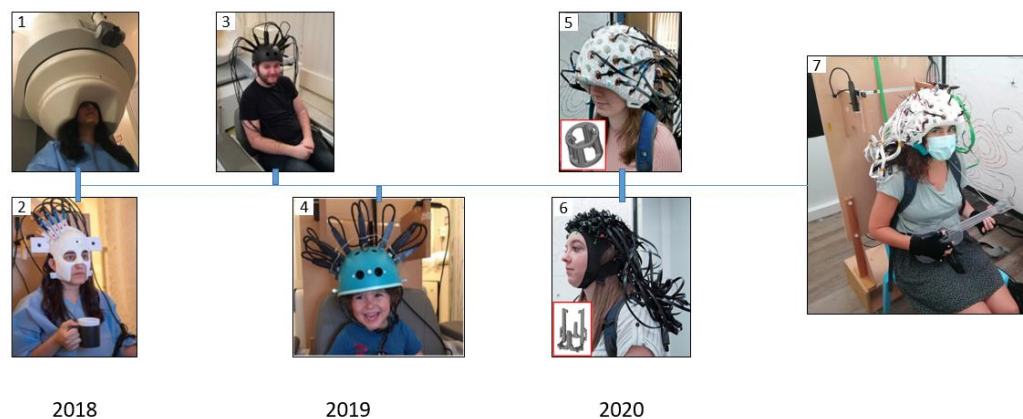


Figure 9.1: Progression towards a whole-head wearable OPM-MEG system. 1) CTF MEG system. 2) Proof-of-principle OPM-MEG system from Boto et al. (2018). 3) Adult bike helmet. 4) Child's bike helmet. 5) Rigid whole-head helmet. 6) Flexible whole-head cap. 7) Rigid whole-head, motion robust wearable OPM-MEG system.

Figure 9.1 shows the progression of the wearable OPM-MEG system over the course of the work presented in this thesis. Figure 9.1 (1) shows a CTF cryogenic MEG system, which represents the state-of-the-art that is already used in research and clinical groups around the world. Figure 9.1 (2) shows the wearable prototype system developed by Boto et al. and represents the

‘jumping off’ point for the work in this thesis. The system held the sensors rigidly on the scalp with accurate knowledge of the locations and orientations of the sensors using the scanner-cast design. Bi-planar nulling coils (Holmes et al., 2018) either side of the participant also allowed natural movements to be performed while being scanned. However, only a maximum of 13 sensors placed over the right motor cortex could be used, and the bespoke nature of the scanner-cast prevented multiple participants from being scanned. The scanner-cast was also too heavy and intimidating for children.

Chapter 4 showed in simulation how a wearable system for use in paediatric populations could be designed, and how such a system compared to the current state-of-the-art cryogenic systems. Due to the adaptability of the sensors to head size and shape, as well as the decrease in scalp-to-sensor distance, significant advantages were demonstrated. This chapter also demonstrated the efficacy of using a generic helmet design (the bike helmet design shown in Figure 9.1 (3)) that can fit multiple participants and, by devising a co-registration technique, can still effectively perform source localisation. Chapter 5 expanded on this work to provide the first experimental demonstration of a system with lifespan compliance (Figure 9.1 (4)) that could robustly detect beta-band modulation in young children, teenagers, and adults alike even when participants were performing natural movements such as playing a musical instrument.

In Chapter 6, we improved upon the principles of the bike helmet prototype and designed a rigid helmet with whole-head coverage (Figure 9.1 (5)). We also investigated the use of a flexible EEG-style cap (Figure 9.1 (6)), and devised new co-registration methods for each design, each bringing their own associated co-registration errors. By comparing the effect of these errors in simulation, we showed that a rigid helmet offers a more robust source reconstruction due to the a priori knowledge of sensor locations and orientation relative to each other. Chapter 7 then showed an experimental

comparison between the two, as well as a cryogenic system, using a paradigm that elicits motor beta and visual gamma modulation to demonstrate whole-head coverage and the ability to detect two simultaneously active brain regions.

Finally, in Chapter 8 we combined the whole-head system with a naturalistic motor learning paradigm to explore the changes in the motor related beta band modulation in relation to the participant's performance (Figure 9.1 (7)), simultaneously exploiting the motion robustness, high fidelity data, and the whole-head coverage offered by our OPM-MEG system.

9.1 Future work

The main aim of the OPM-MEG work at Nottingham is to reach a fully commercial system that can be readily used by research and clinical groups around the world, and that can supersede the current cryogenic systems, which are typically too expensive and unsuited for wide-scale uptake. Such a system has been presented in Chapter 8, and commercialisation of the system is currently underway. However, there are still many avenues to explore with this technology before the MEG community (and wider neuroscience community) can gain confidence in and adopt OPM technology.

First, we must further develop the generic helmet. At 1.7 kg (when 50 sensors are placed in the helmet), it is currently too heavy for children to wear and can quickly become uncomfortable even for adult participants. The helmet also suffers from reasonably large sensor-to-scalp distances (1.9 mm to 26.0 mm, with a median of 7.2 mm for a representative adult male)²⁰ over certain brain regions. Continued work will refine this design to create a helmet with a

²⁰ Though this is still significantly smaller than for a cryogenic MEG system (13.1 mm to 38.8 mm for the same participant (median 26.7 mm)).

comfortable weight that can be worn for longer periods of time without causing discomfort, as well as create novel sensor mounts that can allow sensors to travel radially to be in direct contact with the scalp (Zetter et al., 2019). Eventually, such a helmet could become the standard for OPM-MEG, allowing for consistent acquisition across all age groups.

Chapter 5 was limited in its demonstration of lifespan compliance by the low sensor count, thus only the sensorimotor cortices were covered. By developing a rigid helmet with whole-head coverage that is suitable for children, new information can be gleaned over the development of the human brain. While it may certainly be possible to use a refined generic helmet design (as described in the previous paragraph) that has been adapted for children (i.e. made smaller and lighter), there are potential issues with cross-talk and spatial harmonics that must be considered. In the scaling down of the helmet from adult-sized to child-sized, two approaches can be taken: 1) keep the number of sensors in each the same; or 2) keep the sensor spacing the same. If the number of sensors are kept the same, the spacing between the sensors will reduce which could in turn cause greater cross-talk between the sensors (Roberts, 2020). If the spacing is kept the same, there are fewer sensors used in the smaller helmet and certain spatial harmonics may be missed (Iivanainen et al., 2019a; Tierney et al., 2019b).

The motion robustness of the system paves the way for a new approach to neuroscientific research. Novel paradigms that were previously impossible to implement due to movement constraints can now offer greater insight into neurodevelopment and brain function. The naturalistic motor learning paradigm presented in Chapters 5 and 8 is a prime example. With the improved OPM-optimised MSRs, as well as improvements in field nulling techniques, the nulled region could eventually cover the majority of the inside of the room, allowing participants to get up and walk around (or even allow infants to crawl around the room). It could also allow for two participants to be scanned

simultaneously as they interact with each other (hyper-scanning, see Figure 9.2 (Left) for an example using cryogenic systems) (Montague et al., 2002; Zhdanov et al., 2015). Such interactions could also be studied between a parent and their child, as shown in Figure 9.2 (Right) in EEG (Wass et al., 2018).

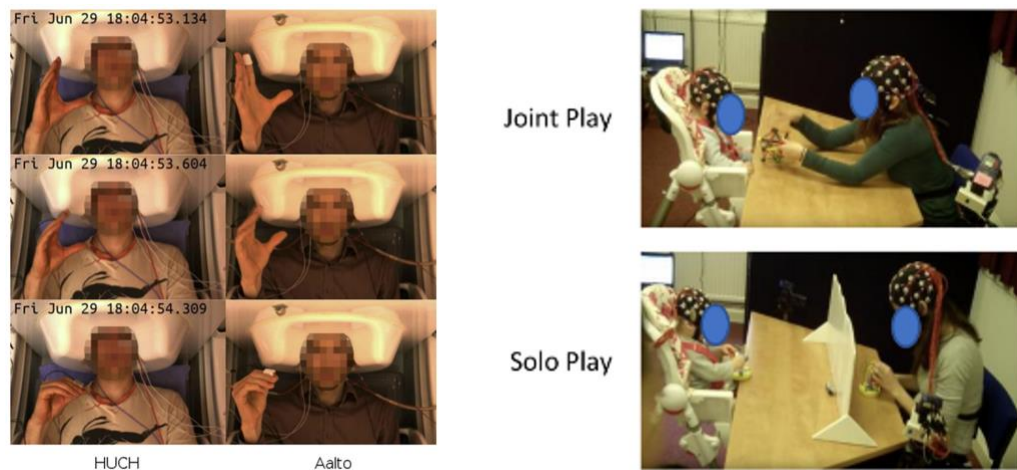


Figure 9.2: Hyper-scanning. Two examples of hyper-scanning. (Left) Two participants being scanned simultaneously in a cryogenic MEG at two separate locations. The participants must mimic each other's movements. (Right) A mother and child being simultaneously scanned with EEG as the child plays either with the mother or on their own.

However, in order for the MEG community to gain confidence in OPM technology, several other tried and tested experiments should also be performed. In this thesis, we have shown several times the ability to detect induced effects within the brain. We have also shown our ability to perform functional connectivity analysis, though proper testing of this would rely on a larger subject cohort and a more rigorous statistical assessment. Direct comparison of the data to cryogenic systems will hopefully show comparable data. Indeed this has already been shown in Boto et al. (Boto et al., 2020) but with only two participants. Several groups over the last few years have demonstrated the ability to detect evoked responses using commercially available OPMs (Borna et al., 2017; Boto et al., 2017), but this has not yet been shown using a wearable whole-head system. Auditory, visual, and somatosensory evoked fields should be explored and compared with a cryogenic system in a similar fashion to the work shown in Chapter 7.

9.2 Final thoughts

The initial aim for this thesis was to design and build the world's first whole-head wearable OPM-MEG system to rival the current state-of-the-art. This, we believe, has been achieved. We have shown a huge development on the initial proof-of-principle system (Boto et al., 2018) and the OPM-MEG instrumentation demonstrated is commercially viable. With some refinement, it could be deployed to research and clinical groups across the world.

It has long been known that today's science becomes tomorrow's technology, and as commercial OPM-MEG becomes reality, it is appropriate to reflect that fundamental physics – our ability to manipulate atoms at the smallest scale – has made this technology possible. Perhaps more exciting, however, is to look to the future. OPM-MEG, coupled with remarkable new techniques for data modelling and novel naturalistic paradigms, will offer researchers a new and unprecedented window on brain function. It will allow a platform to ask, and answer, the biggest questions about the organ that controls our senses, our actions, our thoughts, and our feelings; the organ that, quite simply, makes us human.

References

- Adjamian, P., Barnes, G.R., Hillebrand, A., Holliday, I.E., Singh, K.D., Furlong, P.L., Harrington, E., Barclay, C.W., Route, P.J.G., 2004. Co-registration of magnetoencephalography with magnetic resonance imaging using bite-bar-based fiducials and surface-matching. *Clinical Neurophysiology* 115, 691-698.
- Alem, O., Benison, A.M., Barth, D.S., Kitching, J., Knappe, S., 2014. Magnetoencephalography of Epilepsy with a Microfabricated Atomic Magnetode. *Journal of Neuroscience* 34, 14324-14327.
- Alfhors, S.P., Ilmoniemi, R.J., Hämäläinen, M.S., 1992. Estimates of visually evoked cortical currents. *Electroencephalography and Clinical Neurophysiology* 82, 225-236.
- Allred, J.C., Lyman, R.N., Kornack, T.W., Romalis, M.V., 2002. High-Sensitivity Atomic Magnetometer Unaffected by Spin-Exchange Relaxation. *Physical Review Letters* 89.
- Altarev, I., Fierlinger, P., Lins, T., Marino, M., Nießen, B., Petzoldt, G., Reisner, M., Stuiber, S., Sturm, M., Singh, J., Taubenheim, B., Rohrer, H., Schläpfer, U., 2015. Minimizing magnetic fields for precision experiments. *Journal of Applied Physics* 117.
- 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*.
- Arnal, L.H., Giraud, A.L., 2012. Cortical oscillations and sensory predictions. *Trends in Cognitive Sciences* 16, 390-398.
- Baillet, S., 2017. Magnetoencephalography for brain electrophysiology and imaging. *Nature Neuroscience* 20, 327–339.
- Bardeen, J., Cooper, L.N., Schrieffer, J.R., 1957. Theory of Superconductivity. *Phys. Rev.* 108, 1175.
- Barratt, E.L., Francis, S.T., Morris, P.G., Brookes, M.J., 2018. Mapping the topological organisation of beta oscillations in motor cortex using MEG. *Neuroimage* 181, 831-844.
- 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. *Human Brain Mapping* 38, 2441-2453.
- Batie, M., Bitant, S., Strasburger, J., Shah, V., Alem, O., Wakai, R.T., , 2018. Detection of fetal arrhythmia by using optically pumped magnetometers. *J Am Coll Cardiol Clin Electrophysiol* 4.
- Bell, W.E., Bloom, A.L., 1957. Optical detection of magnetic resonance in alkali metal vapor. *Phys. Rev.* 107, 1559-1565.
- Bentley, J.L., 1980. Multidimensional divide-and-conquer. *Communications of the ACM* 23, 214-229.
- Berger, H., 1933. Über das elektroencephalogram des menschen. *Arch Psychiatr Nervenkr* 99, 555-574.

- Bison, G., Castagna, N., Hofer, A., Knowles, P., Schenker, J.L., Kasprzak, M., Saudan, H., Weis, A., 2009. A room temperature 19-channel magnetic field mapping device for cardiac signals. *Appl Phys Lett* 95.
- Bloch, F., 1946. Nuclear induction. *Phys. Rev.* 70, 460-474.
- Bloch, F., 1953. The principle of nuclear induction. *Science* 118, 425-430.
- Bloom, A.L., 1962. Principles of operation of the rubidium vapor magnetometer. *Appl. Optic.* 1, 61.
- Borna, A., 2020. Non-invasive functional-brain-imaging with an OPM-based magnetoencephalography system. *PLoS ONE* 15.
- Borna, A., Carter, T.R., Colombo, A.P., Jau, Y., Berry, C., McKay, J., Stephen, J., Weisend, M., Schwindt, P.D.D., 2017. A 20-channel magnetoencephalography system based on optically pumped magnetometers. *Physics in Medicine & Biology* 62.
- Boto, E., 2018. *Wearable Magnetoencephalography*. Physics and Astronomy. University of Nottingham.
- Boto, E., Bowtell, R.W., Krüger, P., Fromhold, M., Morris, P.G., Meyer, S., Barnes, G.R., Brookes, M.J., 2016. The Benefits of Atomic Magnetometers for MEG: a Simulation Study. *PLoS ONE* DOI:10.1371/journal.pone.0157655.
- Boto, E., Hill, R.M., Rea, M., Holmes, N., Seedat, Z., Leggett, J., Shah, V., Osborne, J., R., B., Brookes, M.J., 2020. Measuring functional connectivity with wearable MEG. Under review.
- Boto, E., Holmes, N., Leggett, J., Roberts, G., Shah, V., Meyer, S.S., Duque Muñoz, L., 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.
- Boto, E., Meyer, S.S., Shah, V., Alem, O., Knappe, S., Kruger, P., Fromhold, M., Lim, M., Glover, P.M., Morris, P.G., Bowtell, R., Barnes, G.R., Brookes, M.J., 2017. A new generation of magnetoencephalography: Room temperature measurements using optically-pumped magnetometers. *Neuroimage* 149, 404-414.
- Boto, E., Seedat, Z., 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.W., Brookes, M.J., 2019. Wearable Neuroimaging: Combining and Contrasting Magnetoencephalography and Electroencephalography. *Neuroimage* 201.
- Brain-development.org, 2018. Pediatric Brain Atlas. <http://brain-development.org/brain-atlases/pediatric-brain-atlas/>.
- Brant-Zawadzki, M., et al, 1992. MP RAGE: a three-dimensional, T1-weighted, gradient-echo sequence -- initial experience in the brain. *RSNA* 182.
- 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.
- Brookes, M.J., Woolrich, M., Barnes, G.R., 2012. Measuring functional connectivity in meg: a multivariate approach insensitive to linear source leakage. *Neuroimage* 63, 910-920.

- Brookes, M.J., Woolrich, M., Luckhoo, H., Price, D., Hale, J.R., Stephenson, M.C., Barnes, G.R., Smith, S.M., Morris, P.G., 2011. Investigating the electrophysiological basis of resting state networks using magnetoencephalography. *PNAS* 108, 16783-16788.
- BSEN60601-1, 2000. BS EN 60601-1:2006+A12:2014 - Medical electrical equipment. General requirements for basic safety and essential performance.
- Burgess, A.P., Gruzelier, J.H., 1997. Short duration synchronization of human theta rhythm during recognition memory. *NeuroReport* 8, 1039-1042.
- C1055-20, A.I., 2020. C1055-20 Standard Guide for Heated System Surface Conditions that Produce Contact Burn Injuries.
- Cao, L., Hu, Y.-M., 2016. Beta Rebound in Visuomotor Adaptation: Still the Status Quo? *Journal of Neuroscience* 36, 6365-6367.
- Caton, R., 1875. The electrical currents of the brain. *British Medical Journal* 2, 278.
- Chance, B., Zhuang, Z., UnAh, C., Alter, C., Lipton, L., 1993. Cognition-activated low-frequency modulation of light absorption in human brain. *PNAS* 90, 3770-3774.
- Chella, F., Marzetti, L., Stenroos, M., Parkkonen, L., Ilmoniemi, R.J., Romani, G.L., Pizzella, V., 2019. The impact of improved MEG–MRI co-registration on MEG connectivity analysis. *Neuroimage* 197, 354-367.
- Churchill, J.D., Tharps, J.A., Wellman, C.L., Sengelaub, D.R., Garraghty, P.E., 2004. Morphological correlates of injury-induced reorganization in primate somatosensory cortex. *BMC Neuroscience*.
- Claus, S.C., Velis, D., Lopes da Silva, F.H., Viergever, M.A., Kalitzin, S., 2012. High frequency spectral components after Secobarbital: The contribution of muscular origin-A study with MEG/EEG. *Epilepsy Research* 100, 132-141.
- Cohen, D., 1968. Magnetoencephalography: Evidence of Magnetic Fields Produced by Alpha-Rhythm Currents. *Science* 161, 784-786.
- Cohen, D., 1972. Magnetoencephalography: detection of the brain's electrical activity with a superconducting magnetometer. *Science* 175, 664-666.
- 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.
- Dale, M.W., Morley, G.W., 2017. Medical applications of diamond magnetometry: commercial viability. *arXiv:1705.01994*.
- Dang, H., Maloof, A., Romalis, M., 2010. Ultrahigh sensitivity magnetic field and magnetization measurements with an atomic magnetometer. *Applied Physics Letters* 97, 151110.
- de Araújo, D.B., Baffa, O., Wakai, R.T., 2002. Theta Oscillations and Human Navigation: A Magnetoencephalography Study. *Journal of Cognitive Neuroscience* 14, 70-78.
- 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 Nat Acad Sci U S A* 107.
- Du Bois Reymond, E., 1843. Vorläufiger Abriss einer Untersuchung über den sogenannten Froschstrom und umher die elektromotorischen Fische. *Annl Phys* 58, 1-30.
- Fife, A.A., Vrba, J., Robinson, S.E., Anderson, G., et al., 1999. Synthetic gradiometer systems for MEG. *IEEE Transactions on Applied Superconductivity* 9, 4063-4068.
- Florin, E., Baillet, S., 2015. The brain's resting-state activity is shaped by synchronized cross-frequency coupling of neural oscillations. *Neuroimage* 111, 26-35.
- Fox, P.T., Mintun, M.A., Raichle, M.E., Herscovitch, P., 1984. A noninvasive approach to quantitative functional brain mapping with H₂ (15)O and positron emission tomography. *J Cereb Blood Flow Metab* 4, 329-333.
- Fries, P., 2005. A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. *Trends Cogn Sci* 9, 115-125.
- Gaetz, W., Liu, C., Zhu, H., Bloy, L., Roberts, T.P.L., 2013. Evidence for a motor gamma-band network governing response interference. *Neuroimage* 74, 245-253.
- Goldman, D.E., 1943. Potential, impedance, and rectification in membranes. *J Gen Physiol* 27, 37-60.
- Hämäläinen, M.S., Hari, R., Ilmoniemi, R.J., Knuutila, J., Lounasma, O.V., 1993. Magnetoencephalography: theory, instrumentation, and applications to non-invasive studies of the working human brain. *Rev. Mod. Phys* 65, 413-497.
- Hanle, W., 1925. Die magnetische Beeinflussung der Resonanzfluoreszenz. *Ergebnisse der exakten Naturwissenschaften*.
- Hansen, P., Kringelbach, M., Salmelin, R., 2010. MEG: An introduction to methods.
- Hari, R., Hämäläinen, H., Hämäläinen, M.S., Kekoni, J., Sams, M., Tiihonen, J., 1990. Separate finger representations at the human second somatosensory cortex. *Neuroscience* 37, 245-249.
- 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.
- Heinrichs-Graham, E., Wilson, T. W., 2016. Is an absolute level of cortical beta suppression required for proper movement? Magnetoencephalographic evidence from healthy aging. *Neuroimage* 134, 514-521.
- 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., R., B., Slater, R., Brookes, M.J., 2019. A tool for functional brain imaging with lifespan compliance. *Nature Communications* 10.
- 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., R., B., Brookes,

- M.J., 2020. Multi-channel whole-head OPM-MEG: Helmet design and a comparison with a conventional system. *Neuroimage* 219.
- Hillebrand, A., Barnes, G.R., 2011. Practical constraints on estimation of source extent with MEG beamformers. *Neuroimage* 54.
- Hipp, J.F., Hawellek, D.J., Corbetta, M., Siegel, M., Engel, A.K., 2012. Large-scale cortical correlation structure of spontaneous oscillatory activity. *Nature Neuroscience* 15, 884-890.
- Holliday, I.E., et al, 2003. Accuracy and applications of group MEG studies using cortical source locations estimated from participants' scalp surfaces. *Human Brain Mapping* 20, 142-147.
- Holmes, N., Leggett, J., Boto, E., Roberts, G., Hill, R.M., Tierney, T.M., Shah, V., Barnes, G.R., Brookes, M.J., Bowtell R., 2018. A bi-planar coil system for nulling background magnetic fields in scalp mounted magnetoencephalography. *Neuroimage* 181, 760-774.
- Holmes, N., Tierney, T.M., Leggett, J., Boto, E., Mellor, S., Roberts, G., Hill, R.M., Shah, V., Barnes, G.R., Brookes, M.J., R., B., 2019. Balanced, bi-planar magnetic field and field gradient coils for field compensation in wearable magnetoencephalography. *Scientific Reports* 9.
- Homölle, S., Oostenveld, R., 2019. Using a structured-light 3D scanner to improve EEG source modeling with more accurate electrode positions. *Journal of Neuroscience Methods* 326.
- Hoogenboom, N., Schoffelen, J., Oostenveld, R., Parkes, L.M., Fries, P., 2006. Localizing human visual gamma-band activity in frequency, time and space. *Neuroimage* 29, 764-773.
- Hounsfield, G.N., 1973. Computerized transverse axial scanning (tomography): Part 1. Description of system. *The British Journal of Radiology* 46, 1016-1022.
- Iivanainen, J., Mäkinen, A., Zetter, R., Stenroos, M., Ilmoniemi, R.J., Parkkonen, L., 2019a. Sampling theory for spatial field sensing: Application to electro- and magnetoencephalography. *arXiv:1912.05401 [physics.med-ph]*.
- Iivanainen, J., Stenroos, M., Parkkonen, L., 2017. Measuring MEG closer to the brain: Performance of on-scalp sensor arrays. *Neuroimage* 147, 542-553.
- 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* 194, 244-258.
- Iivanainen, J., Zetter, R., Parkkonen, L., 2019c. Potential of on-scalp MEG: Robust detection of human visual gamma-band responses. *Human Brain Mapping* 41.
- Ikeda, H., Leyba, L., Bartolo, A., Wang, Y., Okada, Y.C., 2002. Synchronized Spikes of Thalamocortical Axonal Terminals and Cortical Neurons Are Detectable Outside the Pig Brain With MEG. *Journal of Neurophysiology* 87, 626-630.
- Jaklevic, R.C., Lambe, J., Silver, A.H., Mercereau, J.E., 1964. Quantum interference effects in Josephson tunneling. *Phys. Rev. Lett* 12, 159.

- Johnson, C., Schwindt, P.D.D., Weisend, M., 2010. Magnetoencephalography with a two-color pump-probe, fiber-coupled atomic magnetometer *Applied Physics Letters* 97.
- Johnson, C.N., Schwindt, P.D., Weisend, M., 2013. Multi-sensor magnetoencephalography with atomic magnetometers. *Physics in Medicine & Biology* 58, 6065-6077.
- Josephson, B.D., 1962. Possible new effects in superconductive tunnelling. *Physics Letters* 1, 251-253.
- Jurkiewicz, M.T., Gaetz, W. C., Bostan, A. C., Cheyne, D., 2006. Post-movement beta rebound is generated in motor cortex: Evidence from neuromagnetic recordings. *Neuroimage* 32, 1281-1289.
- Kamada, K., Ito, Y., Kobayashi, T., 2012. Human MCG measurements with a high-sensitivity potassium atomic magnetometer. *Physiological Measurement*.
- 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. *Japanese Journal of Applied Physics* 54, Article number 026601.
- Kastler, A., 1973. The Hanle effect and its use for the measurements of very small magnetic fields. *Nucl. Instrum. Methods* 110, 259-265.
- Kiiski, H.S.M., Ní Riada, S., Lalor, E.C., Gonçalves, N.R., Nolan, H., Whelan, R., 2016. Delayed P100-Like Latencies in Multiple Sclerosis: A Preliminary Investigation Using Visual Evoked Spread Spectrum Analysis. *PLoS ONE* 11.
- Kominis, I.K., Kornack, T.W., Allred, J.C., Romalis, M.V., 2003. A subfemtotesla multichannel atomic magnetometer. *Nature* 422, 596-599.
- Lauterbur, P.C., 1973. Image Formation by Induced Local Interactions: Examples Employing Nuclear Magnetic Resonance. *Nature* 242, 190-191.
- Leong, V., Schilbach, L., 2019. The promise of two-person neuroscience for developmental psychiatry: using interaction-based sociometrics to identify disorders of social interaction. *The British Journal of Psychiatry* 215, 636-638.
- Liao, Y., Akalin Acar, Z., Makeig, S., Deak, G., 2015. EEG imaging of toddlers during dyadic turn-taking: Mu-rhythm modulation while producing or observing social actions. *Neuroimage* 112, 52-60.
- Lodish, H., Berk, A., Zipursky, S.L., Matsudaira, P., Baltimore, D., Darnell, J., 2000. *Molecular Cell Biology*, 4th edition. W. H. Freeman, New York.
- Lopes da Silva, F., 2013. EEG and MEG: relevance to neuroscience. *Neuron* 80, 1112-1128.
- Mäkelä, J.P., Hari, R., 1990. Long-latency auditory evoked magnetic fields. Raven Press.
- 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). *Frontiers in Computational Neuroscience* 12.
- Mansfield, P., Grannell, P.K., 1973. NMR 'diffraction' in solids? . *Journal of Physics C: Solid State Physics* 6.

- 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.
- Muthukumaraswamy, S.D., 2013. High-frequency brain activity and muscle artifacts in MEG/EEG: a review and recommendations. *Frontiers in Human Neuroscience* 7, 138.
- Nardelli, N.V., Krzyzewski, S.P., Knappe, S.A., 2019. Reducing crosstalk in optically-pumped magnetometer arrays. *Physics in Medicine & Biology* 64.
- Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *PNAS* 87, 9868-9872.
- Osborne, J., Orton, J., Alem, O., Shah, V., 2018. Fully integrated, standalone zero field optically pumped magnetometer for biomagnetism. *Steep Disper. Eng. Opto-Atom. Prec. Metrol.*
- Paraskevopoulos, E., Kuchenbuch, A., Herholz, S.C., Pantev, C., 2012. Musical Expertise Induces Audiovisual Integration of Abstract Congruency Rules. *Journal of Neuroscience* 32.
- Pena, M.E., Pearson, C., Goulet, M.P., Kazan, V.M., DeRita, A.L., Szpunar, S.M., Dunne, R.B., 2020. A 90-Second Magnetocardiogram using a novel analysis system to assess coronary artery stenosis in chest pain patients. *IJC Heart & Vasculature* 26.
- Penfield, W., Rasmussen, T., 1950. The cerebral cortex of man. The Macmillan Company, New York.
- Pfeiffer, C., Ruffeux, S., Jonsson, 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.
- Pfurtscheller, G., Lopes da Silva, F., 1999. Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clin Neurophysio* 110, 1842-1857.
- Rabi, I., Zacharias, J., Millman, S., P., K., 1938. A new method of measuring nuclear magnetic moment. *Phys. Rev.* 53, 318.
- Riaz, B., Pfeiffer, C., Schneiderman, J.F., 2017. Evaluation of realistic layouts for next generation on-scalp MEG: Spatial information density maps. *Scientific Reports*.
- Roberts, G., 2020. Magnetoencephalography in a Virtual Environment. *Physics and Astronomy*. University of Nottingham.
- 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., R., B., Brookes, M.J., 2019. Towards OPM-MEG in a virtual reality environment. *Neuroimage* 199, 408-417.
- Robinson, S., Vrba, J., 1998. Functional Neuroimaging by synthetic Aperture Magnetometry. In *Recent Advances in Biomagnetism*, ed. Yoshimoto T, Kotani M, Kuriki S, Karibe H, Nakasato N, Tohoku Univ. Press, Sendai, Japan., 302-305.

- 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: Clinical* 12, 869-878.
- 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.
- Sander, T.H., Preusser, J., Mhaskar, R., Kitching, J., Trahms, L., Knappe, S., 2012. Magnetoencephalography with a chip-scale atomic magnetometer. *Biomedical Optics Express* 3, 981-990.
- Sarvas, J., 1987. Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem. *Phys. Med. Biol.* 32.
- Schwindt, P.D.D., Lindseth, B., Knappe, S., Shah, V., Kitching, J., 2007. Chip-scale atomic magnetometer with improved sensitivity by use of the Mx technique. *Applied Physics Letters* 90.
- Scott, A.C., 1977. *Neurophysics*. Williams and Wilkins, New York.
- Seltzer, S.J., 2008. *Developments in Alkali-Metal Atomic Magnetometry*, Physics. Princeton.
- Shah, V., Hughes, J.K., 2015. Method for Detecting Zero-field Resonance. US 20150212168 A1.
- Shah, V., Knappe, S., Schwindt, P.D.D., Kitching, J., 2007. Subpicotesla atomic magnetometry with a microfabricated vapour cell. *Nature Photonics* 1, 649-652.
- Shah, V., Romalis, M.V., 2009. Spin-exchange relaxation-free magnetometry using elliptically polarized light. *Physical Review A* 80.
- Shah, V.K., Wakai, R.T., 2013. A compact, high performance atomic magnetometer for biomedical applications. *Physics in Medicine and Biology* 58, 8153-8161.
- Stern, O., Gerlach, W., 1922. Der experimentelle Nachweis der Richtungsquantelung im Magnetfeld. *Physik* 9, 349-352.
- Sumner, R.L., McMillan, R.L., Shaw, A.D., Singh, K.D., Sundram, F., Muthukumaraswamy, S.D., 2018. Peak visual gamma frequency is modified across the healthy menstrual cycle. *Hum. Brain Mapp.* 39, 3187-3202.
- Tan, H., Wade, C., Brown, P., 2016. Post-Movement Beta Activity in Sensorimotor Cortex Indexes Confidence in the Estimations from Internal Models. *Journal of Neuroscience* 36, 1516-1528.
- 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., 2019a. Optically pumped magnetometers: From quantum origins to multi-channel magnetoencephalography. *Neuroimage* 199, 598-608.
- Tierney, T.M., Mellor, S., O'Neill, G.C., Holmes, N., Boto, E., Roberts, G., Hill, R.M., Leggett, J., R., B., Brookes, M.J., Barnes, G.R., 2019b. Pragmatic spatial sampling for wearable MEG arrays. *bioRxiv*.

- 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.
- Uhlenbeck, G.E., Goudsmit, S., 1926. Spinning electrons and the structure of spectra. *Nature* 117, 264-265.
- Van Veen, B.D., Buckley, K.M., 1988. Beamforming: a versatile approach to spatial filtering. *IEEE ASSP Magazine* 5.
- Van Veen, B.D., et al, 1997. Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. *IEEE Transactions on Biomedical Engineering* 44, 867-880.
- Vrba, J., Robinson, S., McCubbin, J., 2004. How many channels are needed for MEG? *Neurology & Clinical Neurophysiology*.
- Vrba, J., Robinson, S.E., 2001. Signal Processing in Magnetoencephalography. *Methods* 25, 249-271.
- Vrba, J., Robinson, S.E., 2002. SQUID sensor array configurations for magnetoencephalography applications. *Supercond. Sci. Technol.* 15.
- Wass, S.V., Noreika, V., Georgieva, S., Clackson, K., Brightman, L., Nutbrown, R., Covarrubias, L.S., Leong, V., 2018. Parental neural responsivity to infants' visual attention: How mature brains influence immature brains during social interaction. *PLoS Biology*.
- Whalen, C., Maclin, E.L., Fabiani, M., Gratton, G., 2007. Validation of a method for coregistering scalp recording locations with 3D structural MR images. *Human Brain Mapping* 29, 1288-1301.
- Wilson, T.W., Heinrichs-Graham, E., Becker, K.M., 2014. Circadian modulation of motor-related beta oscillatory responses. *Neuroimage* 102, 531-539.
- Xia, H., Baranga, A.B.A., Hoffman, D., Romalis, M.V., 2006. Magnetoencephalography with an atomic magnetometer. *Applied Physics Letters* 89.
- Zetter, R., Iivanainen, J., Parkkonen, L., 2019. Optical Co-registration of MRI and On-scalp MEG. *Scientific Reports* 9.
- Zhdanov, A., Nurminen, J., Baess, P., Hirvenkari, L., Jousmäki, V., Mäkelä, J.P., Mandel, A., Meronen, L., Hari, R., Parkkonen, L., 2015. An Internet-Based Real-Time Audiovisual Link for Dual MEG Recordings. *PLoS ONE*.