EXAMINING EXECUTIVE FUNCTION AND ITS RELATIONSHIP WITH LANGUAGE OUTCOME IN CHILDREN WITH AND WITHOUT COCHLEAR IMPLANTS: A BEHAVIOURAL AND FUNCTIONAL NEAR-INFRARED SPECTROSCOPY STUDY

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

FEBRUARY 2022

ABSTRACT

While cochlear implants allow many infants to develop appropriate language skills, the ability of individual children to understand speech varies widely. Established evidence suggests that neurocognitive processes contribute to variable language outcome in paediatric cochlear implant (CI) recipients. The cross-sectional and longitudinal experiments reported in this thesis aimed to investigate the association between executive function (EF) and language performance in normal-hearing (NH) and deaf-implanted children, in addition to the ability of behavioural-EF evoked brain activation and correlates of fronto-temporal cortical connectivity to predict future EF and language outcome.

Parent-reported EF skills were significantly associated with language performance in both NH children and paediatric CI users of preschool age. This relationship was significantly stronger in children with CIs compared with their NH peers. Behavioural EF task-evoked cortical activations, measured using functional near-infrared spectroscopy (fNIRS), were acquired from both cohorts of preschool aged children. Whilst performance on behavioural EF tasks was not associated with language ability, a significant correlation between the amplitude of EF task-evoked activation overlying left prefrontal regions and language performance was observed in NH participants. Interestingly, no association was found between parent-reported EF skills and performance on behavioural

EF tasks. Phase Transfer Entropy (PTE) analysis was employed to estimate fNIRS correlates of fronto-temporal directed connectivity. Correlates of both top-down and bottom-up directed connectivity acquired from NH toddlers were able to significantly predict future EF performance, that was in turn associated with language outcome. Furthermore, correlates of bottom-up directed connectivity in NH infants and toddlers were able to directly predict language ability.

The COVID-19 pandemic had an adverse effect on the recruitment of participants to experiments within this thesis. Furthermore, a small sample size for CI users prevented an examination of the association between fNIRS correlates of behavioural EF, cortical connectivity and language outcome in this cohort. However, the current results not only highlight the importance of higher-order top-down processes in language development, but they also support the current theory that such EF mechanisms are potentially more influential in deaf individuals. Furthermore, these findings demonstrate the potential of fNIRS as a brain-imaging tool that is uniquely well-suited for use in cochlear implantation. Future applications of this technology could help explain individual variability in CI outcome and to deliver intervention, such as EF rehabilitation strategies, where required at an earlier stage in a child’s life.

In March 2019, the COVID-19 pandemic induced a mandatory pause in cochlear implantation procedures across the United Kingdom. To minimise the period of auditory deprivation in pre-lingually deaf children, a collaborative project was performed in which novel Personal Protective Equipment (PPE) options were evaluated. The recommendations from this project led to the safe restart of cochlear implantation procedures at the National Health Service (NHS) Hospital Trust affiliated with the primary research site and continue to support the national and international delivery of CI services throughout COVID-19.

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Harrison, S.C., **Lawrence, R.J.,** Hoare, D.J., Wiggins, I.M., & Hartley, D.E.H. (2021). Use of Functional Near-Infrared Spectroscopy to Predict and Measure Cochlear Implant Outcomes: A Scoping Review. *Brain Sci,* 11, 1439. http://doi.org/10.1016/j.heares.2020.108155

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CONFERENCE PRESENTATIONS

Lawrence, R. J., Wiggins, I.M., Hartley, D.E.H. (2021). Examining Executive Function and its Relationship with Language Outcome in Paediatric Cochlear Implant Recipients: A Behavioural and Functional Near-Infrared Spectroscopy (fNIRS) Study. *Oral presentation at the 15th European Symposium of Paediatric Cochlear Implantation,* Virtual Conference.

Lawrence, R. J., Wiggins, I.M., Hartley, D.E.H. (2021). Examining Executive Function and its Relationship with Language Outcome in

Paediatric Cochlear Implant Recipients: A Behavioural and Functional Near-Infrared Spectroscopy (fNIRS) Study. *Oral presentation at the 2021 Conference on Implantable Auditory Prostheses (CIAP),* Virtual Conference.

Lawrence, R. J., Wiggins, I.M., Hartley, D.E.H. (2021). Examining Executive Function and its Relationship with Language Outcome in Paediatric Cochlear Implant Recipients: A Behavioural and Functional Near-Infrared Spectroscopy (fNIRS) Study. *Oral presentation at the Annual Meeting of the British Association of Paediatric Otorhinolaryngology*, Birmingham, UK.

Lawrence, R. J., Wiggins, I.M., Hartley, D.E.H. (2021). Using functional near-infrared spectroscopy (fNIRS) to objectively measure executive function and its relationship to speech and language outcomes in children with and without cochlear implants. *Oral presentation at the Annual Meeting of the British Cochlear Implant Group*, Virtual Conference.

Lawrence, R. J., Wiggins, I.M., Hartley, D.E.H. (2020). Using functional near-infrared spectroscopy (fNIRS) to objectively measure executive function and its relationship to speech and language outcomes in children with and without cochlear implants. *Poster presentation at the Annual Meeting of the British Cochlear Implant Group*, Nottingham, UK.

Lawrence, R. J., Wiggins, I.M., Anderson, C.A., Davies-Thompson, J. & Hartley, D.E.H. (2019). Cortical correlates of speech intelligibility measure using functional near-infrared spectroscopy (fNIRS). *Poster presentation at the 2019 Conference on Implantable Auditory Prostheses (CIAP),* California, USA.

ACKNOWLEDGEMENTS

Firstly, I would like to sincerely thank my supervisor Professor Douglas Hartley for not only enabling me to undertake this PhD in Nottingham, but also for his investment in and incredible support throughout my clinical academic career. Secondly, my immense thanks go to my co-supervisor Dr Ian Wiggins for his continual support and guidance throughout all aspects of this research.

I am indebted to Jayne Ramirez Inscoe and Angela Maxwell for their role in acquiring language performance data and to Professor Martha Ann Bell for sharing her immense expertise with experimental design. Many thanks go to Dr Guangting Mai for his support with fNIRS data analysis and to Professor Pádraig Kitterick for his advice throughout the PhD. I would also like to thank Dr Carly Anderson for training me in the use of fNIRS, but more importantly for her continual academic and personal support during the more difficult times.

I would like to thank all of those from The Nottingham Auditory Implant Programme (NAIP), including Professor Gerry O'Donoghue, Mr Andrew Marshall, Miss Priya Achar, Tracey Twomey and Susan Johnson for their help with the recruitment of cochlear implant recipients. Many thanks to Kate Hanvey and Justine Maggs at the Midlands Hearing Implant Programme, Lise Henderson at the Manchester Cochlear Implant Programme, Mr David Selvadurai and Sharmila Patel at the St George's Hospital Cochlear Implant Programme in addition to The University of Southampton Auditory Implant Centre for their collaboration with the studies within this PhD and support with recruitment. Thank you also to the Cochlear Implanted Children's Support (CICS) Group and the National Deaf Children's Society. Many thanks also to Sandra Smith for her help with the recruitment of normal-hearing children from the National Institute of Health Research (NIHR) Nottingham Hearing Biomedical Research Centre (NHBRC) database.

My gratitude also extends to Dr Kevin O'Donoghue, Professor Richard Hague, Laura Mitchell, Zoe Lycett-Ranson, Professor Susan Anderson and Dominik Siwek in addition to all other members of the research team involved in the Personal Protective Equipment (PPE) project. Their joint efforts led to the restart of local Cochlear Implant (CI) services and continue to facilitate the ongoing delivery of evidence-based clinical care to paediatric patients during COVID-19.

Lastly, my immense thanks go to my partner James and my family for all their love, encouragement and unwavering support that has enabled me to be where I am today.

This thesis is dedicated in loving memory to Liam Treadwell, 3rd January 1986 – 23rd June 2020, an excellent Grand National winning jockey, but more importantly a kind, warm and much-loved friend who lived by the motto "never get so busy making a living that you forget to make a life"

.

AND

To Graham Parker, 23rd December 1955 - 13th February 2022, an outstandingly kind, witty and true gentleman who will forever remain in my heart.

FINANCIAL SUPPORT

This PhD was supported by a Clinical Research Training Fellowship (CRTF) award from the UK Medical Research Council (September 2018 – August 2021).

DECLARATION

I certify that this is my own work, except where indicated by referencing. No part of this thesis has been submitted elsewhere for any other degree or qualification.



28/02/2022

Rachael Lawrence Date

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LIST OF ABBREVIATIONS

AC	Auditory Comprehension (PLS-5^{UK})
ADHD	Attention Deficit Hyperactivity Disorder
AGP	Aerosol Generating Procedure
ANSD	Auditory Neuropathy Spectrum Disorder
ASD	Autism Spectrum Disorder
BA	Brodmann Area
BRIEF	Behavior Rating Inventory of Executive Function
CCC-2	Children's Communication Checklist – 2nd Edition
CDI	Communicative Development Inventory
CDI-WGCDI	Words and Gestures (MacArthur-Bates CDI)
CDI-WCDI	Words and Sentences (MacArthur-Bates CDI)
CI	Cochlear Implant
COVID-19	Coronavirus Disease 2019
DC	Directed Connectivity
DCCS	Dimensional Change Card Sorting
DCM	Dynamic Causal Modelling
DLPFC	Dorsolateral Prefrontal Cortex
EC	Expressive Communication (PLS-5^{UK})
EEG	Electroencephalogram
EF	Executive Function
$ETCO_2$	End-Tidal Carbon Dioxide
FC	Functional Connectivity
$FiCO_2$	Fractional Inspired Carbon Dioxide
fMRI	Functional Magnetic Resonance Imaging
fNIRS	Functional near-infrared spectroscopy
GA	General Anaesthesia
GCC	General Communication Composite (CCC-2)
GEC	Global Executive Composite (BRIEF)
GLM	General Linear Model
HA	Hearing Aid
HbO	Oxygenated Haemoglobin
HbR	Deoxygenated Haemoglobin

HCW	Healthcare Worker
HR	Heart Rate
HRA	Health Research Authority
HRF	Haemodynamic Response Function
IC	Inhibition Control
IPC	Infection Prevention Control
LMM	Linear Mixed Model
LPFC	Lateral Prefrontal Cortex
MDT	Multidisciplinary Team
MEG	Magnetoencephalography
NAIP	Nottingham Auditory Implant Programme
NH	Normal-hearing
NHBRC	Nottingham Hearing Biomedical Research Unit
NHS	National Health Service
NHSP	Newborn Hearing Screening Programme
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NUH	Nottingham University Hospitals
O_2	Oxygen
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PHE	Public Health England
PIC	Participant Information Centre
PLS-5^{UK}	The Preschool Language Scales – Fifth edition – UK
PPE	Personal Protective Equipment
PTA	Pure-Tone Average
PTE	Phase Transfer Entropy
RCS	Royal College of Surgeons
ROI	Region of Interest
SCI	Scalp Coupling Index
SD	Standard Deviation
SEM	Standard Error of Mean
SIDC	Social Interaction Deviance Composite (CCC-2)
SLI	Specific Language Impairment
SNHL	Sensorineural Hearing Loss

STC	Superior Temporal Cortex
UK	United Kingdom
USA	United States of America
VDU	Visual Display Unit
VLPFC	Ventrolateral Prefrontal Cortex
WHO	World Health Organization
WISC-V	Wechsler Intelligence Scale for Children–Fifth Edition
WM	Working Memory

1. THESIS OVERVIEW

1.1 INTRODUCTION

A cochlear implant (CI) is an implantable neuroprosthetic device that provides a sensation of hearing to severe-to-profoundly deaf individuals. Cochlear implantation has the potential to significantly improve language skills, especially when it occurs in early infancy (A. E. Geers et al., 2003; Niparko et al., 2010). Despite advances in CI device technology, a high level of individual variability in paediatric language outcome is observed (Niparko et al., 2010; Semenov et al., 2012; Tobey et al., 2013). Certain clinical, audiological and socioeconomic characteristics (amongst other factors) have consistently been associated with improved language outcome. These include shorter duration of deafness, better pre-implanted pure-tone average (PTA) hearing thresholds and a higher level of parental education (A. Geers et al., 2003; Geers, 2002; A. E. Geers et al., 2003; Kronenberger et al., 2020). However, even after accounting for these predictor characteristics, substantial variability in individual CI outcome remains (Pisoni et al., 2010). Emerging evidence suggests that neurocognitive processes, notably executive function (EF), should be considered important contributors to the observed variability in language outcome following paediatric cochlear implantation (Beer et al., 2014; Kronenberger, Beer, et al., 2014; Kronenberger et al., 2020).

Although various models of EF have been proposed, amongst them is the consensus that it consists of a set of higher-order, top-down cognitive processes involved in coordinating, planning and completing desired actions (Miyake et al., 2000). At the cortical level, EF is typically associated with activation within prefrontal brain regions (Diamond, 2013). Executive function is generally accepted to consist of three core elements: 1) inhibition control (IC), the ability to suppress specific thoughts or behaviour; 2) working memory (WM), temporarily holding and processing information in immediate memory to guide reasoning and decision-making and; 3) cognitive flexibility (CF), the ability to switch between a mental or behavioural task in response to changing demands (Miyake et al., 2000). Evidence shows that pre-lingually deaf children with CIs are two to five times more likely than normal-hearing (NH) children to have deficient EF skills (Kronenberger, Beer, et al., 2014). Furthermore, considerable individual differences in EF have been observed amongst pre-lingually deaf children who receive a CI early in life (Kronenberger, Colson, et al., 2014), which has contributed to the hypothesis that the observed variability in language outcome may be accounted for by differences in neurocognitive processing (Conway et al., 2011; Geers, Strube, et al., 2011).

Although an association between EF and language is well-established (Fuhs & Day, 2011; Kuhn et al., 2016), the direction of causation remains uncertain in both NH children and children with

CIs. The literature commonly describes EF and language to be reciprocally and bidirectionally related in both typically-developing and deaf individuals, particularly in early childhood (Singer & Bashir, 1999). However, most of these studies have been cross-sectional in design, hence are unable to detect causation. Interestingly, findings from a more recently performed longitudinal study demonstrate that language delays cannot fully explain differences in EF development between children with CIs and their NH peers during preschool ages, yet EF skills can predict subsequent language performance in children with CIs (Kronenberger et al., 2020).

Executive function in preschool age children has been shown to improve with implementation of specific environmental and behavioural interventions (Blair & Raver, 2014; Diamond & Lee, 2011), hence there may be value in integrating such treatments into existing speech and language therapy regimens (Kronenberger et al., 2020). Early identification of children (both with and without a hearing loss) who are at risk of EF delay has the potential to improve the effectiveness of any implemented rehabilitation approach. Currently, clinical assessments of EF are reliant on behavioural measures and since very young children are often difficult to assess with behavioural techniques, there may be a delay of many years before less favourable EF outcome is detected. The implementation of objective measurements of EF may avoid the problem of solely relying on behavioural methods alone. Furthermore, the relationship between typical brain development

and behvaioural EF, particularly in early childhood, is not fully established and hence limits the understanding of how and why deficits in EF emerge more commonly in children affected by severe-to-profound sensorineural hearing loss (SNHL). An understanding of the neurodevelopmental mechanisms underlying the emergence of EF in both the normal-hearing and auditory-deprived brain may enable the identification of objective neural markers of EF performance, which may offer further insight into the observed variability in paediatric CI language outcome. Well-established objective neuroimaging techniques are either: 1) limited in their compatibility with a CI device; 2) challenging for children in the absence of general anaesthesia (GA) or sedation, or; 3) not safe for repeated testing. However, one promising solution is functional near-infrared spectroscopy (fNIRS), a non-invasive optical imaging technique that can be safely and repeatedly used to objectively study cortical activation in NH children and children with CIs (Sevy et al., 2010).

It has been proposed that maturation of the prefrontal cortex (PFC) during the second half of infancy supports the emergence of cognitive processes, including EF (Colombo & Cheatham, 2006; Diamond, 1990). A plethora of neuroimaging studies in children with typically-developing brains demonstrate a relationship between behavioural EF performance and activity within the PFC (Aron et al., 2014; Konishi et al., 1998; Laird et al., 2005; Monchi et al., 2001; Wager & Smith, 2003). Furthermore, infant resting-state cortical

connectivity patterns have been shown to predict both later EF (Broomell et al., 2019) and language ability (Mundy et al., 2003). With respect to the auditory-deprived brain, evidence suggests that congenital deafness affects the development of neural connections between auditory and higher-order cortical areas (Sharma et al., 2009) such as the PFC. Notably, severe-to-profoundly deaf children have been shown to exhibit differences in resting-state connectivity in superior temporal regions compared with their NH peers (Tibbetts et al., 2011; S. Wang et al., 2019; Xia et al., 2017). This evidence highlights the importance of imaging superior temporal regions, in addition to prefrontal areas of the cortex, during both the resting- and EF-task induced state when examining neural mechanisms underlying EF.

This thesis takes advantage of fNIRS imaging using it to evaluate correlates of cortical activity in both typically-developing children and children with CIs. Specifically, it consists of two main face-to-face experiments: 1) a cross-sectional fNIRS study involving children aged 4 to 6 years old, and; 2) a longitudinal fNIRS study in children aged 6 to 48 months. Each study involved a group of NH children and children with bilateral CIs, with the longitudinal experiment following children with a severe-to-profound SHNL from pre- to post-implantation. Hearing subjects were recruited to investigate the association between EF and language in typically-developing children, and not for the purpose of performing quantitative statistical between group comparisons with CI

participants. During both experiments, fNIRS measurements of cortical activation in prefrontal and superior temporal regions were acquired whilst participants performed a behavioural EF task. A period of resting-state brain activity was also recorded. Parent-reported measures of EF and language performance were also achieved for each participant. The overall aim of this work was to understand the development of behavioural and cortical correlates of EF in both NH children and children with CIs, and whether such measures can help explain the observed variability in language outcome amongst paediatric CI users. The longitudinal study was designed to not only evaluate how behavioural EF task-evoked cortical activation and fronto-temporal connectivity change over time and following cochlear implantation, but also whether these factors can predict later behavioural EF and language performance in both NH children and children with CIs.

The progress of this thesis was severely affected by the COVID-19 pandemic, which resulted in a nine month pause in face-to-face research activity. More importantly, cochlear implantation surgeries were temporarily halted at most auditory implant programmes in the United Kingdom (UK) and worldwide due to the COVID-19 international public health emergency. However, continency plans were devised during this thesis work, the most impactful of which involved working with an internationally recognised team of experts that consisted of academics, engineers, surgeons, anaesthetists and operating theatre staff. This collaborative project involved preclinical

and clinical level studies that evaluated novel Personal Protective Equipment (PPE) and Infection Prevention Control (IPC) measures required for the safe restart of CI surgery. The findings of these studies led to the resumption of cochlear implantation procedures at the National Health Service (NHS) Hospital Trust affiliated with the primary research site, which not only minimised the period of auditory deprivation in pre-lingually deaf children, but also facilitated research studies such as the ones included in this thesis to ultimately continue. During the COVID-19 induced mandatory pause in face-to-face research activity, a cross-sectional study was also performed in which parent-reported measures of EF and language were acquired for both NH children and children with bilateral CIs. Aligned with the overall aim of this thesis, this project allowed the investigation into the relationship between EF and language to continue via non-participant facing methodology.

1.2 OVERVIEW OF FOLLOWING CHAPTERS

Chapter 2: Executive Function in the Normal-Hearing and Deaf Child and its Relationship with Language: A literature Review

This chapter presents a review of the literature that is fundamental to this thesis. Firstly, the chapter outlines SNHL and the significance of cochlear implantation and auditory rehabilitation. The chapter presents the evidence on the observed variability in individual paediatric CI language outcome and describes the influence of key clinical characteristics. The chapter emphasises that a large amount

of variance in CI outcome remains unexplained and explores the evidence that EF accounts for a proportion of this observed variability in language performance. The literature exploring the development of behavioural EF in both NH children and children with CIs is discussed, in addition to that examining the relationship between EF and language performance in both cohorts of children. The evidence to date on the neural mechanisms underlying behavioural EF is presented. This chapter identifies that these cortical mechanisms are not fully understood, especially in children with a severe-to-profound SNHL, which largely relates to methodological challenges that preclude repeated neuroimaging in paediatric CI recipients. The technique of fNIRS is presented as a promising solution for examining fronto-temporal connectivity and behavioural EF task-induced cortical activation in all children via appropriately designed studies. This chapter closes by briefly describing the impact that the COVID-19 pandemic had on NHS cochlear implantation services and the progress of this thesis, and finally outlines the overall aims of the thesis and the mitigation steps taken that enabled these objectives to be achieved despite the ongoing pandemic.

Chapter 3: Experiment Designs and Methodology

This chapter describes the design and methodology of the cross-sectional and longitudinal, neuroimaging and behavioural studies of EF conducted with paediatric CI recipients and NH subjects. The chapter outlines the details of participant recruitment, study design

and implemented experimental methods. Responses to age-appropriate behavioural EF tasks were recorded from the prefrontal and superior temporal cortex bilaterally using fNIRS. A period of resting-state brain activity was also measured. Behavioural performance on EF tasks was evaluated. A language assessment by a qualified NHS Speech and Language Therapist was originally scheduled. In January 2020, the outbreak of the novel coronavirus (SARS-CoV-2) led to an international public health emergency that subsequently halted CI surgery at all auditory implant programmes recruiting participants to this thesis work. Prior to the COVID-19 pandemic, the plan for the longitudinal study was to acquire behavioural and neuroimaging measures from NH participants during three separate research sessions over a 12 month period and from children with bilateral severe-to-profound SNHL during four separate research sessions over a similar time frame, following these subjects from pre- to post-implantation. However, an interruption to the timing and frequency of these research sessions (in addition to the plans for assessing language ability) was anticipated. Hence, this chapter describes the action taken to mitigate the effect that COVID-19 had on recruitment to and the progress of both the cross-sectional and longitudinal studies.

The safe resumption of CI surgery at local, national and international auditory implant programmes required novel PPE and IPC solutions to prevent the transmission of the SARS-CoV-2 virus to health care workers (HCWs). This chapter describes the

methodology of both preclinical and clinical level studies that aimed to assess the risk of COVID-19 transmission during CI surgery and how this may be mitigated by potential PPE and IPC solutions. These studies were collaboratively designed and performed by an internationally-recognised team of experts. During the mandatory COVID-19 induced pause in face-to-face cross-sectional and longitudinal fNIRS studies, a cross-sectional study acquiring parent-reported measures of behavioural EF and language was also implemented to maintain the investigation into the relationship between EF and language performance. The details of participant recruitment and methodology for this additional study are also outlined in this chapter.

Chapter 4: The Development of Behavioural Executive Function

This chapter reports on behavioural EF task performance and parent-reported measures of EF in a group of NH children and paediatric CI users. The chapter employs descriptive statistics and bivariate correlation analysis to examine how behavioural EF performance is associated with chronological age from infancy onwards. For children participating in the longitudinal experiment, individual trajectories of performance on behavioural EF tasks over time are presented. The results demonstrate that performance on behavioural EF tasks varies substantially amongst NH children with similar chronological ages. Despite this between-subject variability, most NH participants who were examined on a longitudinal basis

improved their EF performance with increasing age. It was difficult to draw conclusions on behavioural EF task performance in CI users due to the limited sample size of this group. However, a high level of between-subject variability in performance on parent-reported measures of EF was observed for both NH children and paediatric CI users. Importantly, these results suggested that further investigation into behavioural EF, not only in terms of neurodevelopmental mechanisms, but also its potential contribution to variable language outcome in both typically-developing and deaf infants and children is warranted.

Chapter 5: The Relationship Between Executive Function and Language Performance

The first half of this chapter examined the relationship between measures of behavioural EF and language in both NH children and paediatric CI users. Behavioural EF performance was assessed not only via visually-based IC and WM tasks, but also via parent-reported measures. Language ability was initially evaluated via a face-to-face assessment with a qualified speech and language therapist, but due to the impact of COVID-19, parent-reported measures were subsequently implemented. There was no association between performance on the visual behavioural EF tasks and language ability in NH children. Unfortunately, this relationship could not be examined in the CI group due to the limited number of participants that performed the behavioural tasks. However, parent-reported measures of behavioural EF and language were

significantly associated in both groups of children, and interestingly, these measures were more closely correlated in CI users compared with their NH peers. No association was found between parent-reported EF skills and performance on behavioural EF tasks.

The second half of this chapter presents fNIRS measurements of cortical activation to visual IC and WM tasks acquired from NH children and paediatric CI users. Time course analyses within pre-defined prefrontal and superior temporal regions of interest (ROI) confirmed the successful, artefact-free measurement of cortical activation elicited by behavioural EF in both groups of children. Unfortunately, the limited number of CI participants recruited to these experiments prevented formal statistical analysis of EF-evoked cortical activation in this group. However, for NH participants, group-level cortical activation maps are used to display patterns of cortical activation across the bilateral measurement array for each EF task. The chapter employs a ROI analysis using a Linear Mixed Model (LMM) approach to examine the effect of EF task condition, participant age and task performance on cortical activation. Bivariate correlation analysis was also performed to analyse the relationship between cortical correlates of behavioural EF and language performance in NH children. The results demonstrate substantial behavioural EF-evoked cortical activation and that the amplitude of this cortical activity within left prefrontal regions was significantly associated with language performance. With the caveat of a small sample size for CI participants, these

preliminary results raise the possibility that deaf-implanted children have a similar amplitude of visual EF task-evoked cortical activation within prefrontal regions when compared with their NH peers, yet a lower amplitude of such activation in superior temporal regions. This chapter considers the possibility that this lower amplitude of visual IC and WM task-evoked activation within the superior temporal regions of deaf-implanted children is related to the process of neuronal decoupling of prefrontal and auditory areas, leading to a lack of top-down neuronal influence from higher-order prefrontal areas that are demonstrated to be significantly activated during EF tasks. In addition, this chapter introduces the possible implications that neuronal decoupling may have on EF and language processing, thus leading to the subsequent examination of cortical connectivity between prefrontal and auditory brain regions in the following chapter.

Chapter 6: Cortical Connectivity as a Predictor of Future Executive Function and Language Performance

This chapter examines resting-state cortical connectivity and cortical connectivity on EF task-evoked brain activation, between prefrontal and superior temporal regions and the ability of each to predict future EF and language performance. Measures of both EF and language were acquired, on average, 12 months after fNIRS brain imaging. The application of Phase Transfer Entropy (PTE) methodology for the analysis of fNIRS data allowed the direction of any connectivity that was predictive of EF and language ability to be

estimated. Regression analyses revealed that bottom-up resting-state connectivity between right superior temporal and right prefrontal regions of NH infants and toddlers was predictive of future language performance. Furthermore, both top-down and bottom-up connectivity between left prefrontal and left superior temporal regions following EF task-evoked brain activation predicted future EF performance in NH toddlers that was, in turn, associated with language outcome. The development of intra-hemispheric fronto-temporal connectivity appeared to peak at around two years of age in typically-developing children, indicating that neuronal connections between EF and language processing regions are mature by the third year of life. Insufficient recruitment of paediatric CI users to the longitudinal experiment means that connectivity between prefrontal and superior temporal cortices of deaf children, in addition to the impact of cochlear implantation on such connectivity, remains inadequately investigated. However, descriptive analysis of connectivity data acquired from a CI participant both pre- and post-implantation, suggested that left hemispheric fronto-temporal connectivity was weaker for this CI user compared with NH peers. Furthermore, top-down and bottom-up connectivity between left prefrontal and superior temporal regions was observed to increase in the months following CI device insertion.

Chapter 7: Recommendations on Personal Protective Equipment Required for Cochlear Implant Surgery During COVID-19

This chapter presents the results of a preclinical study that assessed the risk of SARS-CoV-2 transmission to HCWs during simulated CI surgery via an objective assessment of mastoid-drill induced contamination. The spread of the contaminated mixture of droplets, bone, blood and tissue was found to extend further than previously reported in the literature. However, spread of contamination was substantially reduced via the use of a novel drape tent over the surgical field. Novel PPE solutions were also evaluated during this preclinical study. An evidence and systematic risk-based approach was implemented to assess the various PPE solutions in terms of their impact on communication, vital physiological parameters, visual acuity and fields, and acceptability to surgeons. The findings of this preclinical study led to Nottingham University Hospitals (NUH) NHS Trust, the Hospital Trust affiliated with the primary research site, implementing recommendations on the PPE and IPC measures required for CI surgery during the COVID-19 pandemic. These recommendations enabled the resumption of CI surgery at NUH NHS Trust. Following implementation of these PPE and IPC recommendations, the first ten CI and other mastoid surgeries were clinically evaluated. All ten surgical cases were performed safely and successfully. However, the findings within this chapter highlight that the majority of PPE is based on the size and characteristics of European and North American males. This chapter concludes that a

'one-size-fits-all' approach to PPE provision is not always compatible with certain cohorts of the population, such as female and ethnic minority HCWs.

Chapter 8: Summary and Discussion

This chapter presents a summary of the main findings of the thesis, including: i) behavioural EF varies substantially amongst typically-developing and deaf infants and children; ii) parent-reported behavioural EF is significantly associated with language performance and this relationship is significantly stronger in children with CIs compared with their NH peers; iii) the ability of fNIRS to longitudinally measure behavioural EF-evoked cortical activation in both NH children and paediatric CI users; iv) the amplitude of behavioural EF-evoked cortical activation overlying the left prefrontal cortex is significantly associated with language performance in NH children and; v) correlates of fronto-temporal connectivity are able to predict future EF and language for NH infants and toddlers. The chapter provides a general discussion and interpretation of these results, including limitations of the current research. Directions for future research are proposed and closing conclusions are made.

2. EXECUTIVE FUNCTION IN THE NORMAL-HEARING AND DEAF CHILD AND ITS RELATIONSHIP WITH LANGUAGE: A LITERATURE REVIEW

2.1 INTRODUCTION

Cochlear implantation can significantly improve language skills, especially when children are implanted very early in life (Niparko et al., 2010). However, the degree to which an individual benefits can vary immensely amongst paediatric CI recipients and remains unpredictable (Niparko et al., 2010; Semenov et al., 2012; Tobey et al., 2013). Healthcare professionals are therefore currently unable to accurately counsel individual parents on the clinical benefit and language skills that their child will eventually achieve. A greater understanding of the factors that are fundamental to the variability in CI language outcome would be immensely beneficial to this parental counselling process and help clinicians to appropriately manage patient and parental expectations. This chapter firstly reviews the research to date on the factors that are known to influence paediatric CI outcome and their predictive value in terms of language performance. A growing body of evidence suggests that neurocognitive processes, notably EF, may be responsible for a proportion of the variance in CI language outcome that remains after accounting for the most common predictor clinical characteristics (Beer et al., 2014; Kral et al., 2016; Kronenberger, Beer, et al., 2014; Kronenberger et al., 2020). Evidence of

behavioural and cortical correlates of EF development in both NH children and children with a severe-to-profound SNHL is reviewed. In particular, the relationship between EF and language performance is examined with an emphasis on whether causation can be established. This chapter also outlines the current challenges of measuring behavioural EF-evoked brain activation and cortical connectivity, especially following cochlear implantation, with conventional neuroimaging techniques. The promise of fNIRS for studying the cortical mechanisms underlying EF development over time and following CI device insertion is discussed.

2.2 VARIABILITY IN COCHLEAR IMPLANT OUTCOME

2.2.1 Sensorineural Hearing Loss and Cochlear Implantation

Permanent bilateral severe-to-profound hearing loss affects approximately 1 in 1000 newborns (Butcher et al., 2019). The prevalence of hearing loss (including all degrees from mild through to profound) increases through childhood and by age 18 years, one in every five children are affected (J. Wang et al., 2019). Multiple aetiologies play a role including head trauma, exposure to ototoxic medication and the delayed onset of genetic hearing loss. It is well acknowledged that hearing loss has a negative impact upon multiple aspects of an individual's life including speech and language, cognition, education, employment and social integration (World Health Organisation, 2021).

Hearing loss can be classified as sensorineural, conductive or mixed in nature. Sensorineural hearing loss (SNHL) is the most common

type of hearing loss, with its cause lying in either the cochlea and its associated structures, the auditory nerve or the central auditory pathway. Severe-to-profound SNHL is most frequently caused by either damage to or a deficiency in cochlear hair cells (Moore, 2007). Consequently, acoustic signals are unable to appropriately simulate spiral ganglion neurons of the auditory nerve. Transmission of acoustic information from the peripheral to the central auditory system is therefore substantially reduced. For it to be perceived as sound, incoming acoustic information needs to be processed in auditory brain regions, hence an individual with severe-to-profound SNHL has either a diminished ability or complete inability to perceive auditory speech stimuli.

In terms of auditory rehabilitation, evidence from behavioural and neuroimaging studies suggests that bilateral acoustic input to the central auditory system of individuals with SNHL, when compared with unilateral input, leads to significantly better language outcomes (Litovsky & Gordon, 2016; Sarant et al., 2014). Although appropriate for some individuals with SNHL, amplification of acoustic signals provided by acoustic hearing aids (HAs) is typically

Figure removed

Figure 2.1: A cochlear implant device and how it works. An external microphone (1) receives acoustic information from the environment. A speech processor (2) then converts the acoustic information into digital information that is transmitted via a magnetic coil transmitter (3) to the internally implanted receiver and stimulator (4). The received digital information is then converted into electrical signals by the receiver, which are then transmitted down the electrode array (5) implanted within the cochlea. The spiral ganglion neurons of the auditory nerve are then stimulated, hence the damaged or deficient cochlea hair cells bypassed, and electronic signals are transmitted to the central auditory system via the auditory nerve. Processing of the electronic signals by auditory brain regions enables the perception of sound. Image taken and adapted from (Lieu et al., 2020).

ineffective for children with a bilateral severe-to-profound SNHL. Bilateral CI insertion is often a more appropriate option for these individuals due to the device's ability to directly stimulate the spiral ganglion neurons of the auditory nerve and provide a partially restored, albeit artificial, sensation of hearing (see Figure 2.1 for a more detailed explanation). In the UK, simultaneous bilateral cochlear implantation is considered a cost-effective rehabilitation option for children with severe-to-profound SNHL who do not receive adequate benefit from acoustic hearing aids (NICE, 2019). The National Institute for Health and Care Excellence (NICE) have produced guidance on the audiological criteria that should be met by all potential CI recipients. Severe-to-profound deafness is defined as hearing sounds that are louder than 80 decibels hearing level (dB HL) at two or more frequencies of 0.5, 1, 2, 3 and 4 kilohertz (kHz) bilaterally without HAs. For children, adequate benefit from HAs is defined as speech, language and listening skills appropriate to age, developmental stage and cognitive ability. The 2019 NICE recommendations also state that all individuals should

undergo a multidisciplinary team (MDT) assessment, a part of the candidacy process that is jointly performed by specialists including audiologists, surgeons, psychologists and teachers of the deaf.

The benefit gained from cochlear implantation can be assessed using a variety of age- and developmentally-appropriate outcome measures, which most commonly include: 1) assessments of expressive and receptive language development using evidence-based clinical tools such as the Preschool Language Scales (Zimmerman et al., 2014); 2) audiological measures of speech perception acquired through word recognition scores on the Bamford-Kowal-Bench (BKB) sentence test (Bench et al., 1979; Peixoto et al., 2013), and; 3) parent-reported measures of language ability using standardised communicative development inventories (CDIs) such as the MacArthur Bates CDI (Fenson et al., 2006). Other outcomes include measures of quality of life (NICE, 2019), the ability to integrate into mainstream education (NICE 2019; Geers, Brenner, et al., 2011), an increased awareness or recognition of environmental sounds, and in older recipients an ability to communicate using the telephone and appreciate music (Cooper, 2006). As the primary benefit of cochlear implantation is the acquisition of hearing, with a further expectation that this will improve communication, empirical research studies commonly define the primary measure of paediatric CI outcome as performance on some form of age- and developmentally-appropriate speech perception or language assessment. This thesis

defines ‘CI outcome’ as the level of expressive and/or receptive language ability in a child following cochlear implantation, with the specific assessment used to measure this level of performance detailed where appropriate.

Children who receive CIs at a very young age often demonstrate a substantial improvement in their spoken language trajectory (A. E. Geers et al., 2003; Niparko et al., 2010), with many children scoring in or near average ranges for language skills when aged between eight and nine years old (A. E. Geers et al., 2003). However, language outcome following cochlear implantation in children is far from uniform, with many children achieving near-normal expressive language ability in quiet environments, whereas others perform sub-optimally in this domain (Eisenberg et al., 2007; Ganek et al., 2012; Niparko et al., 2010; Tobey et al., 2013). It is perhaps not that surprising that a variation in individual CI outcome is observed due to the heterogeneity in many clinical characteristics such as age at implantation, duration of deafness, pre-implant residual hearing, aetiology of deafness, presence of medical comorbidities, socioeconomic status and parental education. Interestingly, even after accounting for the most common clinical characteristics, substantial and unexplained variability persists. The evidence relating to this inter-individual variability is reviewed in the following sections.

2.2.2 Factors Affecting Cochlear Implant Outcome in Children

2.2.2.1 Age at implantation, duration of deafness, pre-implant residual hearing

There is a vast amount of evidence to support improved expressive and receptive language development in children who are implanted before the age of three years (Nicholas & Geers, 2006, 2007; Tao et al., 2018; Ubrig et al., 2019; Wu et al., 2006). Improved outcomes in children implanted below this age threshold are thought to be accounted for by a sensitive period in the development of auditory cortical function (Sharma et al., 2005; Sharma et al., 2007). This sensitive period reportedly occurs before the age of three and a half years and reflects a time during which the central auditory system is particularly plastic and capable of normal maturation (Lazard et al., 2012; Sharma et al., 2005). This auditory cortical maturation may still be achieved in deaf children for whom early CI insertion is able to provide appropriate auditory stimulation (Sharma et al., 2005; Sharma et al., 2007). Whilst cochlear implantation inside of this sensitive period for the auditory system leads to less variable outcome than those who are implanted after three years of age, inter-individual variability still exists amongst children who are implanted early in life. This observed variability may be partly explained by cross-modal reorganisation of the auditory cortex. Cross-modal reorganisation is characterised by activation of defined cortical areas by one or more sensory modality outside of what would usually stimulate those regions of the brain. This reorganisation appears to commence in the fetal brain and may be

irreversible even despite early implantation (Giraud & Lee, 2007; Lee et al., 2007). It is well-established that non-implanted deaf individuals develop takeover of their auditory cortex by visual stimuli. Pre-lingual deafness, defined as deafness that occurs prior to oral language acquisition, has been particularly associated with visual cross-modality and the subsequent adverse effect on auditory speech perception (Nishimura et al., 1999). After the auditory sensitive period, in the absence of ongoing auditory stimulation, auditory areas lack not only intrinsic connections but also extrinsic connections with higher-level cognitive regions and processes (Kral et al., 2005; Sharma et al., 2009). In deaf children who are implanted at an older age, although auditory stimuli may reach the primary auditory cortex, functional decoupling of auditory and prefrontal regions may negatively affect speech processing (Giraud & Lee, 2007). Furthermore, children who receive CIs later in life may experience a greater degree of cross-modal reorganisation with auditory stimuli preferentially activating visual and other cortical areas rather than specific auditory pathways, leading to adverse language outcome (Sharma et al., 2007; Sharma et al., 2009).

The introduction of newborn hearing screening programmes (NHSP) has led to a substantial decrease in the age at which SNHL is diagnosed. A UK based study showed the median age at which a hearing loss was identified through objective hearing tests forming part of the national screening programme was ten weeks of age, compared with an age of 12 to 20 months when behavioural

distraction testing was performed by a health visitor (Bamford et al., 2005). The UK NHSP therefore facilitates early cochlear implantation and numerous studies have provided evidence for improved language development in children implanted before 12 months of age (Litovsky & Gordon, 2016). Therefore, where possible, cochlear implantation generally takes place in the first year of life. However, the UK NICE guidance on cochlear implantation was recently updated in 2019 and the audiological criteria for candidacy was subsequently relaxed. Hence, hundreds more children are now eligible for CIs on the NHS each year, many of which are likely to be older. As a result of their increased age at implantation, evidence suggests that these older children will experience more variable language outcome.

Better pre-implant unaided PTA thresholds (Geers, 2006) and shorter duration of deafness (Geers, Strube, et al., 2011; O'Donoghue et al., 2000) are also associated with improved language outcome. However, the duration of deafness is often more difficult to establish, especially if it is gradual in onset or commences and progresses in children after newborn screening.

2.2.2.2 Aetiology of Deafness and Presence of Medical Comorbidities

The cause of a severe-to-profound SNHL can be difficult to establish, a challenge that is reflected in a study which documented the aetiology as 'unknown' in 35% of over 280 paediatric CI recipients (Boons et al., 2012). Although the aetiology of deafness

does not have a significant impact on the CI candidacy clinical assessment process (Summerfield & Marshall, 1995), certain diagnoses have been associated with adverse CI outcome. One such aetiology is meningitis due to its association with ossification of the cochlea. As a consequence of the abnormal bone growth, electrode insertion may be more difficult and hence incomplete, potentially leading to poorer CI outcome (Rotteveel et al., 2005). A study designed to assess the relationship between the improvement in language scores and the aetiology of hearing loss in CI recipients showed that children with an associated syndromic diagnosis (i.e. Usher's, CHARGE, Waardenburg syndrome) had significantly lower improvement scores at four to five years after implantation than children with either a hereditary-non syndromic cause for their hearing loss (i.e. connexin 26 mutation), or an unknown diagnosis (Rajput et al., 2003). Although children with a SNHL and associated medical comorbidities can benefit from CI insertion (Wiley et al., 2008), the outcome achieved may not match those gained by their CI-using peers who lack additional health diagnoses, hence the potential benefit must be balanced against the risks of surgical implantation in each individual (Nasralla et al., 2018). Other factors associated with more variable CI outcome include developmental anomalies in the inner ear such as incomplete partition of the cochlea (Morlet et al., 2017), Auditory Neuropathy Spectrum Disorder (ANSD) (Daneshi et al., 2018) and congenital cytomegalovirus (CMV) infection (Lyutenski et al., 2017; Philips et al., 2014).

2.2.2.3 Socioeconomic Status and Parental Education

Access to resources upon which CI outcome partially relies, such as rehabilitation services and support for communication methods, may be affected by socioeconomic status. Such access may be particularly problematic for families living outside of countries with dedicated auditory implant programmes and universal healthcare provision (Sharma et al., 2020). Nevertheless, if resources are geographically accessible, the annual income of a CI recipient's family does not affect the benefit gained from cochlear implantation (Ching et al., 2010; Peixoto et al., 2013). Maternal education and greater maternal sensitivity during parent-child interaction have been associated with higher speech perception scores (Cowan et al., 2018; Quittner et al., 2013), with children of university educated mothers scoring higher than those of mothers who received less than 12 years of schooling (Ching et al., 2010).

2.2.3 Predictive Models of Cochlear Implant Outcome

Many studies have further explored the established variability in paediatric CI outcome using multiple linear regression models. Interestingly, despite accounting for the most common predictor characteristics, considerable and unexplained variability persists. Boons et al. (2012) divided some of these common predictors into three main categories to determine the amount of variance in expressive and receptive language performance attributable to each category. These three categories consisted of: (1) auditory factors,

including age at diagnosis of SNHL and age at implantation; (2) child-related factors consisting of gender, aetiology and additional disabilities, and; (3) environmental factors including education, parental involvement and mode of communication. Three years after implantation, the total model accounted for 52% of the variance in receptive language scores and 58% of the variance in expressive language scores. Age at implantation was the most substantial of all the predictive factors in the model, responsible for 32% and 36% of the receptive and expressive language performance respectively. Tobey et al. (2003) entered similar predictors into a model, yet additionally incorporated implant characteristics such as the number of active electrodes. Despite accounting for these additional factors, 47% of the variance in speech perception remained unexplained by their model (Tobey et al., 2003). Although these predictive models have significant limitations such as being heterogenous in both design and recruited subjects, they do individually highlight that a large amount of variance in CI outcome (over 40%) remains unaccounted for.

2.2.4 Summary

The above review of the literature highlights that despite the identification of a wide range of factors that can influence the benefit that an individual child receives from cochlear implantation, considerable variability in CI outcome remains unexplained. As stated in the United States National Institutes of Health Consensus Development statements on CIs in adults and children, individual

differences and variability in language outcome remains a significant clinical problem that is yet to be adequately addressed (U.S. Department of Health & Human Services, 1995). An increased understanding of the mechanisms that underlie variable CI outcome would not only enable the development of new interventions, but also facilitate healthcare professionals to better pre-operatively counsel patients and parents about how much benefit an individual is likely to receive from CIs. Neurocognitive factors such as EF are widely considered to have an association with language development (Kronenberger and Pisoni, 2018; Rönnberg et al., 2008), however the exact nature of the relationship between EF and language remains controversial. Nonetheless, evidence is rapidly emerging to suggest that neurocognitive processes such as EF may contribute to the variability in benefit gained from CIs, and furthermore, that such factors should be clinically assessed alongside the more common characteristics known to affect CI outcome.

2.3 THE SIGNFICANCE OF EXECUTIVE FUNCTION IN VARIABLE LANGUAGE OUTCOME

2.3.1 Overview of Executive Function

Executive function describes the higher-order cognitive processes required to achieve planned and goal-directed actions (Diamond, 2013). Although generally accepted to consist of three main elements: 1) working memory (WM); 2) inhibition control (IC), and; 3) cognitive flexibility (CF) (Miyake et al., 2000), additional

components of EF have been proposed that include self-monitoring and organisational skills (Kral et al., 2016; Kronenberger et al., 2020). Despite not being described in the Miyake et al. (2000) model, many researchers consider attention to be fundamental to EF development (Garon et al., 2008). In the typically-developing child, EF reportedly starts to develop during infancy with rapid changes occurring during the preschool years that continue to develop through adolescence and adulthood (Anderson, 2002; Espy et al., 2001; Zelazo et al., 2013). A strong correlation is shown to exist between early childhood EF and subsequent academic achievement, socio-economic and health status, criminal activity rates and substance abuse during adulthood (Casey et al., 2011; Diamond et al., 2007; Eakin et al., 2004; Moffitt et al., 2011). Furthermore, deficient EF skills are associated with a plethora of childhood disorders including attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) (Barkley, 2006; (Rosenthal et al., 2013).

A deficit in auditory and other sensory stimuli is reported to have negative consequences for EF development due to it, and other neurocognitive processes, being dependent on multiple cortical regions working collaboratively (Pisoni et al., 2010; (Kral et al., 2016) (see Figure 2.2). Evidence from animal studies suggest that congenital deafness functionally decouples the primary auditory cortex from higher-order cortical areas, a process that alters both top-down and bottom-up based functions such as attention,

Figure removed

Figure 2.2: An illustration of the neural interactions between the human auditory cortex and higher-order cortical areas. The green arrows reflect bottom-up connections and the red arrows top-down connections. A deficit in auditory and language experience is reported to both directly and indirectly affect neurocognitive processing and executive function in children with cochlear implants (Kronenberger & Pisoni, 2018). Image taken from Kral et al. (2016).

learning and memory (Kral & Sharma, 2012). Therefore, its perhaps not that surprising that pre-lingually deaf children with CIs are two-to-five-times more likely than NH children to have deficient EF skills (Kronenberger, Beer, et al., 2014). Interestingly, considerable individual differences in EF have also been observed amongst pre-lingually deaf children who receive a CI early (Kronenberger, Colson, et al., 2014).

It is not apparent how the rehabilitation of deafness via cochlear implantation affects the development of EF. This matter is further complicated by the aforementioned observation that EF in CI users varies considerably (Lyxell et al., 2008). Variable performance in EF has been observed as early as during the preschool years in paediatric CI recipients (Beer et al., 2014), a period during which the development of EF and language skills are potentially related. This suggests that the observed diversity in EF may account for a wide range of performance in language outcome in children with CIs.

2.3.2 Executive Function and its Relationship with Language Performance

It is well established that EF and language are highly connected however, it has been notoriously difficult to decipher the exact

relationship between the two. Auditory experience is proposed to support EF through the provision of temporal patterns that are essential for pattern detection, WM and controlled attention (Conway et al., 2009). Furthermore, auditory input reportedly facilitates the acquisition of expressive language, that subsequently not only enables goal-directed information to be held within WM, but also allows the use of self-talk to inhibit and regulate behaviour (Alderson-Day & Fernyhough, 2015; Doebel et al., 2018). Conversely, elements of EF such as WM, IC and sustained attention have been shown to support language acquisition (Horn et al., 2004; Rönnberg et al., 2008). Executive function reportedly regulates listening effort that subsequently results in greater listening efficiency (Kronenberger et al., 2020). This increased listening proficiency is proposed to allow for more effective language processing, an important requirement for encoding degraded input from a CI (Kronenberger et al., 2020; Pichora-Fuller et al., 2016).

The aforementioned evidence supports the commonly accepted theory that EF and language are reciprocally and bidirectionally related (Singer & Bashir, 1999). However, others report the influence of language on later EF, and vice versa, to be non-signficant (Gooch et al., 2016). An explanation for a lack of clarity on the nature of the relationship between EF and language perhaps lies in the observation that the majority of studies investigating this association (in both NH children and children with CIs) are cross-sectional in nature. In the limited longitudinal studies involving

typically-developing children, some report that early language appears to predict later EF skills more than the other way around (Kuhn et al., 2016; Petersen et al., 2015). In contrast, one longitudinal study concluded that lanaguge delays cannot fully explain differences in EF development between children with CIs and their NH peers, yet EF skills can predict subsequent language performance in paediatric CI users (Kronenberger et al., 2020). Since the majority of deaf children are reported to have cognitive ability akin to their NH peers (Marschark & Hauser, 2008), deaf children offer a unique opportunity to disentangle EF and language skills since language difficulties in this cohort of children have a sensory and not cognitive basis (Botting et al., 2017). A study by Botting et al. (2017) concluded that language mediated EF ability in deaf and NH children (aged 8 years), but the reverse pattern was not observed. The findings of this study align with Zelazo and Frye (1998)'s complexity and control theory, which proposes that the manipulation of cognitive processes via internal representations is enabled by specific rules derived from language learning, hence language is a driver of EF abilities in children (Zelazo & Frye, 1998). Furthermore, a longitudinal study involving deaf non-implanted children aged 6 to 11 years reported that vocabulary predicted scores on nonverbal EF tasks performed two years later, but not the reverse (A. Jones et al., 2020).

Hearing, speech and language are closely related yet separate elements, hence it is difficult to separate the effect of hearing

(auditory input and experience) from the effect of language (linguistically structured and processed input) on EF. Hall et al. (2018) used a between-groups design involving children aged 5 to 12 years across 3 groups: (1) NH participants; (2) deaf native signers who had access to American Sign Language from birth, and; (3) oral CI users who did not have full access to language prior to cochlear implantation. Measures included both parent-reported Behaviour Rating Inventory of Executive Function (BRIEF) and behavioural performance-based assessments of EF. Results indicated that favourable EF performance does not require auditory experience per se and that language proficiency whether that be in sign or in speech, is more important for development of EF skills. Deaf native signers showed no evidence of problems in performance-related EF compared to typically-developing children, although there were statistically significant differences relative to NH controls on two BRIEF scales (IC and WM). Furthermore, deaf native signers performed no worse than CI users and interestingly many of their parent-reported EF skills were significantly better. The authors of this study therefore concluded that deafness itself does not account for poor EF, rather a lack of early access to language has a stronger impact (Hall et al., 2018). The findings of a study by Marshall et al. (2015) align with those of Hall et al. (2018), whereby a group of deaf children who were native users of British Sign Language performed at the same level as their hearing peers on two non-verbal WM tasks. The results of both these studies are consistent with reports that deaf children who acquire sign language

from their deaf parents develop typical EF skills (Morgan & Dye, 2020). Marshall et al. (2015) also reported that vocabulary scores predicted performance on the two non-verbal WM tasks and subsequently concluded that language skills, whether spoken or signed, play a critical role in the development of EF. Interestingly, a retrospective study that compared paediatric CI recipients who had either deaf parents (hence native sign language users) and hearing parents reported that deaf native signers outperformed those with hearing parents on measures of speech perception, speech production and lanaguge development at 3, 6 and 12 months post-implantation (Hassanzadeh, 2012). It has previously been implied that early experience with visual language has a negative impact on CI outcome via the disruption of crossmodal integration of auditory and visual information which subsequently compromises the ability of the auditory cortex to process spoken language (Nishimura et al., 1999; Giraud and Lee, 2007). In contrast, the findings of Hassanzadeh (2012) suggest that favourable CI outcome depends upon audiovisual integration skills and language input during early sensitive periods, both of which subsequently enable effective cognitive development in deaf children (Lyness et al., 2013) which in turn appears to further support language development.

Kronenberger et al. (2020) acknowledged that there was a lack of longitudinal studies in preschool children (aged 3 to 6 years) with CIs, hence examined the development of EF and language skills over time in this cohort. The authors reported that measures of

language predicted the verbal WM element of EF in both CI and NH samples. However, performance on visual WM tasks was able to predict language scores in both cohorts of children, whereas verbal WM predicted later language ability in CI users only. This latter study supports the theory that language and EF are reciprocally and bidirectionally related (Ylvisaker and Debonis, 2000; Singer & Bashir, 1999) in CI recipients, at least when considering the domain of verbal WM.

Making a distinction between the verbal and visuospatial elements of WM may therefore be of significance when it comes to examining the association between EF and language. Baddeley & Hitch (1974) describe a three-component model of WM which postulates that WM consists of a control system known as the central executive and two storage systems: 1) the visuospatial sketchpad, and; 2) the phonological store within a phonological loop. In this model, verbal auditory input is temporarily held in a store within the phonological loop, whereas visuospatial information is briefly maintained in the visuospatial sketchpad. The phonological loop is suggested to facilitate the acquisition of auditory language by: 1) providing a temporary representation for new phenome sequences, and; 2) supporting learning through a silent articulatory or verbal rehearsal process akin to internal or so called subvocal speech (Baddeley, 2003) (see Figure 2.3). The verbal and visuospatial components of WM are reported to be behaviourally distinguishable entities in children as young as 4 years old, and aligned with Baddeley's model

(Baddeley, 2003), verbal and visuospatial information are also reportedly stored within the aforementioned domain-specific systems at this chronological age (Alloway et al., 2006; Pickering et al., 1998). Furthermore, there is evidence to suggest that a domain-general component (compatible with the central executive) is similarly responsible for the overall processing of both verbal and visuospatial information in typically-developing preschool aged children (Alloway et al., 2006). However, children with specific language impairment are known to perform less desirably on verbal WM tasks, but within the normal range on visuospatial measures of WM (Alloway & Archibald, 2008). A stronger correlation between verbal WM and language outcome has been observed in CI users compared with NH peers, and conversely, an association between visuospatial WM and language skills has been demonstrated in NH peers but not CI users (Kronenberger, Colson, et al., 2014). This suggests that atypical populations may have deviant WM storage and/or processing within the phonological loop, which perhaps explains the specific bidirectional and reciprocal relationship between verbal WM and language observed in deaf-implanted children (Kronenberger et al., 2020). However, further research is needed to scrutinise this potential relationship as many of these observations result from cross-sectional correlation analysis rather than studies of a longitudinal design, the latter enabling a prediction of causality.

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Figure 2.3: The three-component model of working memory. i) This model, proposed by Baddeley and Hitch (1974), suggests that working memory consists of a control system, the central executive and two storage systems known as the visuospatial sketchpad and the phonological loop. **ii)** The flowchart illustrates the proposed function of the phonological loop. An auditory stimulus undergoes phonological analysis (a) and is subsequently temporarily held in short-term storage (STS) within the inferior parietal lobe (b). Thereafter, the auditory information passes through an output buffer located in the premotor cortex (c) where it is either available for expressive speech or recall and recycling through an articulatory rehearsal process analogous with silent, internal subvocal speech. However, visual information may be analysed, temporarily stored (d) and then recoded as verbal material by grapheme-to-phoneme conversion (e). This recoded information is then able to gain access to the phonological store through rehearsal. Taken and from Baddeley (2003) and Vallar & Papagno (2002).

2.3.3 Summary

Evidence tells us that EF supports academic and socioeconomic achievements in addition to promoting good overall health. Furthermore, the literature suggests that EF may develop in the absence of auditory experience when visual speech and language are the primary mode of communication from an early age. It is commonly accepted that language and EF are reciprocally and bidirectionally related. However, evidence suggests that language has a strong effect on future executive processing in deaf children and with respect to CI users specifically, it may be that such a bidirectional relationship only exists between specific domains of EF, namely WM processes dedicated to verbal information. Experiments of a longitudinal design, involving infants and preschool age children, are best placed to examine such a relationship as they can observe the association as it develops over time and specifically during the sensitive period of hearing and language acquisition. However, longitudinal studies in both NH children and children with CIs are currently lacking. It is for this reason that one of the

experiments within this thesis specifically observes the development of behavioural EF overtime and how this relates to language outcome in both NH and deaf-implanted children. Prior to designing this longitudinal study, it was necessary to review the literature to establish the evidence-based methods available for measuring behavioural EF in both cohorts of children.

2.4 BEHAVIOURAL EXECUTIVE FUNCTION IN THE NORMAL-HEARING AND DEAF-IMPLANTED CHILD

2.4.1 Behavioural Executive Function in the Normal-Hearing Infant

Executive function is claimed to manifest itself in infancy as a solitary process that matures and differentiates with development (Garon et al., 2008). Although the exact nature of this initial sole element is unclear, Garon et al. (2008) suggest that three differentiated individual components of EF share a common executive attention component that is the precursor for WM to initially develop, followed by IC, and then CF. Individual differences in infant attention are not only hypothesised to reflect the speed of information processing, but are also claimed to be related to later cognitive abilities such as memory, language and intelligence (Cuevas & Bell, 2014).

The measurement of EF during infancy is challenging as task performance depends on participants' motor skills as well as their language ability (Cuevas et al., 2018). The most extensively used

EF task in typically-developing and NH infants is the delayed-memory search or delayed-response (DR) task, on which a significant amount of infant behavioural EF research is based (Cuevas & Bell, 2010; Diamond & Doar, 1989; Pelphrey et al., 2004; Wiebe et al., 2010). The DR task is a nonverbal EF task that is reportedly dependent on the dorsolateral prefrontal cortex (DLPFC) in both human and animal subjects (Diamond, 1990; Pelphrey & Reznick, 2004). Research using a variant of the DR task, the A-not-B task, has shown comparable developmental progression in performance across tasks (Diamond, 1985; Diamond & Doar, 1989). In the A-not-B task, a child participant watches as a desirable object such as a toy is hidden in different locations. A brief delay is then imposed while the child's visual attention to the hiding location is distracted, after which the child is allowed to search for the object. After successful searching in one location (A), the hiding location is changed to location (B). An A-not-B error is deemed to occur if a child continues to search at the incorrect location (A) on reverse trials (B). Successful task performance therefore requires visuospatial WM to temporarily hold the object location within memory and IC to ignore previously rewarded responses (Diamond, 1990).

The A-not-B task can be made more challenging by not only increasing the number of A trials prior to reversal to location B, but also the delay between hiding the object and allowing the child to search (Cuevas & Bell, 2010; Miller & Marcovitch, 2015). The A-not-

B task with invisible displacement has been used to further enhance difficulty and enable suitability for children in the second year of life (Wiebe et al., 2010) and is typically used from 15 months of age upwards (Cuevas & Bell, 2014; Diamond et al., 1997). Cuevas & Bell. (2014) utilise the A-not-B with invisible displacement task up to the age of 24 months, whilst (Diamond et al., 1997) extend its use even further to 30 months. In this version of the task, as described by Cuevas & Bell. (2014), the infant watches as an attractive toy is hidden in a central location under a non-transparent cup. The cup containing the hidden toy is moved to one side (location A) of the testing table and the child given sufficient time to visualise the final location of the cup on the table. An opaque barrier is then placed in front of the cup and a 5 second delay is imposed, during which and behind the barrier, a second identical cup (location B) is placed on the table. The barrier is then removed and the child allowed to search for the toy under the cup. Once the infant achieves two correct same-side findings, the hiding location is reversed (A-A-B) to provide an inhibitory challenge.

Numerous longitudinal behavioural research studies have provided an evidence-based understanding of the emergence and development of EF in NH and typically-developing infants. Although individual differences in the maximum delay for accurate searches in the A-not-B task are observed, there is a general linear trend in performance between 7.5 and 12 months with an increase of 2 to 3 seconds per month in the delay required to produce errors in either

task. Findings also indicate that by around 8 months, improvements in A-not-B performance are observed with about half of infants exhibiting success on reversal trials with minimal delay (Bell & Fox, 1992; Diamond, 1985). A fundamental level of WM and IC is observed around 10 months, with most children achieving success on reversal trials with minimal delay and some succeeding with longer delays (Diamond, 1985). Table 2.1 provides an overview of the evidence-based behavioural tasks for assessing EF in the infant population.

Table 2.1: An overview of infant executive function tasks

Task	EF Components	Description	Age	Reference(s)
Delayed-Response (A-not-B)	WM & IC	An infant must find an object in one of multiple locations after a delay and inhibit searching in previously rewarded locations.	4.5 months +	Cuevas & Bell, (2010); Diamond et al., (1997); Pelphrey et al., (2004); Wiebe et al., (2010)
Delayed-Response (A-not-B) with Invisible Displacement	WM & IC	An infant must find an object in one of multiple locations after a delay and inhibit searching in previously rewarded locations. An extra challenge is added with invisible displacement	15 months +	Wiebe et al., (2010); Cuevas & Bell, (2014); Diamond et al., (1997)

WM = working memory; IC = inhibition control. Taken and adapted from Cuevas et al., (2018)

2.4.2 Behavioural Executive Function in the Normal-Hearing in Early Childhood

During the second year of life, in addition to exhibiting improvements in more advanced aspects of the A-not-B task, children begin to develop competence for other EF tasks. The tongue task, performed in individuals as young as 22 months, is an inhibition task that requires a child to hold an edible object on their tongue without eating it for time intervals of 10, 20 and finally 30 seconds (Kochanska et al., 2000). The crayon delay task (Calkins, 1997) is typically used from 24 months (Morasch & Bell, 2011) and involves presenting children with a box of crayons and a blank piece of paper. Before a child touches the crayons, the experimenter tells the child that he/she needs to leave the room and instructs the child not to touch the crayons, box, or paper until he/she returns. The experimenter then leaves the room for 60 seconds and subsequently scores the behaviour upon returning. The mommy/me task (Bell & Wolfe, 2007) is a stroop-like IC and WM task that is typically performed from 24 months onwards (Broomell et al., 2019). The child is instructed to remember two rules and exhibit IC by performing a subdominant response. During the mommy/me task, the child is instructed to say "mummy" when shown a picture of himself or herself and to say "me" when shown a picture of the mother. Cuevas et al. (2012) performed the mommy/me task on a group of children aged 4 years old and approximately 2 years later, a parent-reported measure of their children's EF skills was acquired

using the BRIEF questionnaire. A regression analysis revealed later parent-reported EF skills were associated with higher pre-kindergarten levels of mommy/me task performance.

Other stroop-like IC tasks include the day-night task (Gerstadt et al., 1994) and yes-no task (Bell & Wolfe, 2007). The day-night task can be performed from 36 months onwards and involves instructing children to say "day" in response to a picture of a moon with some stars and "night" in response to picture of a sun. The yes-no task is similar to the day-night task and is performed in children upwards of 48 months. Children are instructed to say "yes" when the experimenter shakes their head no and to say "no" when the experimenter nods their head yes. Inhibition control can also be tested with a Go/NoGo task in which participants are asked to respond to targets (Go trials) and to avoid making a response to non-targets (NoGo trials) i.e. when a series of different coloured spaceships appear sequentially on a computer screen (Smith et al., 2017). The N-back task can be used to assess WM and involves presenting participants with black shapes (e.g. star, circle) on a white screen and instructing them to push the response button only if they see the same shape twice in a row. Both the Go/NoGo and N-back tasks are commonly used paradigms in behavioural research and are typically used in children aged 48 months and older (Smith et al., 2017).

Extensive research has shown the CF element of EF to manifest itself later in development than WM and IC, probably from 36

months onwards, and appears to develop rapidly during the preschool years (see Table 2.2). The Dimensional Change Card Sort (DCCS) task is widely used to examine CF (Moriguchi et al., 2010; Zelazo, 2006) and involves children sorting cards that have two dimensions, such as colour and shape (i.e. red stars, blue squares). There are two phases to the task: 1) a pre-switch, and; 2) a post-switch phase. During the pre-switch phase, children are asked to sort cards according to one dimension such as colour. During the post-switch phase, children are asked to sort the cards according to the other dimension such as the shape. It has been shown that most 3 year old children correctly perform the pre-switch phase, but show difficulty with the post-switch phase (Moriguchi, 2012; Zelazo, 2006), whereas by 4 years of age most children correctly sort the cards according to the second dimension (Doebel & Zelazo, 2015).

2.4.3 Behavioural Executive Function in Children with Cochlear Implants

Children with pre-lingual deafness and CIs are two-to-five times more likely than NH children to have substandard performance in most domains of EF (Kronenberger, Beer, et al., 2014). Studies utilising both parent-reported measures of EF, such as behaviour checklists including BRIEF (Beer et al., 2014; Beer et al., 2010), and task-based performance outcomes (Figueras et al., 2008; Kronenberger, Colson, et al., 2014) have observed non-implanted deaf children and children with CIs to perform below the level of hearing children. Figueras et al. (2008) found that both CI and HA

users aged between 8 to 12 years performed worse than NH controls on measures of IC, WM and CF (Figueras et al., 2008). Kronenberger, Colson, et al. (2014) reported that long-term CI users with a mean age of 4.9 years performed worse than a sample of age- and IQ-matched NH controls on behavioural measures of verbal WM and IC (Kronenberger, Colson, et al., 2014). Interestingly, and consistent with the findings by Figueras et al. (2008), the two groups tested by Kronenberger, Colson, et al. (2014) did not differ on visuospatial WM, an EF skill proposed by some researchers to unlikely need support from long-term linguistic knowledge.

The studies mentioned above have been all performed in long-term CI users, hence older children and/or adults. However, research studies involving younger paediatric CI users have also been performed. Beer et al. (2014) performed a cross-sectional study involving two groups of children aged between 3 and 6 years old. Group one consisted of 24 children who had CIs prior to 36 months of age and group two was made up of 21 NH children. All were assessed with visuospatial WM and IC tasks in addition to parent-reported measures of EF. Children with CIs showed significantly poorer performance on IC and visuospatial WM tasks compared with their NH peers. Interestingly, when data was controlled for language, differences in performance measures of EF remained yet differences in parent-reported measures of EF were no longer significant.

The literature differs on whether visuospatial WM is substantially affected in deaf-implanted children. However, deficits in verbal WM have been identified in numerous studies involving paediatric CI users (Figueras et al., 2008; Kronenberger, Colson, et al., 2014; Kronenberger, Pisoni, Henning, et al., 2013). The association of verbal WM with language outcome is consistently observed to be stronger in CI users than NH controls (Kronenberger, Colson, et al., 2014; Kronenberger, Pisoni, Harris, et al., 2013; Pisoni et al., 2011). The Digit Span Forward subtest, that forms part of the Wechsler Intelligence Scale for Children® - Fifth Edition (WISC-V; Wechsler, 2014), is considered by some researchers to be a well-validated measure of verbal WM in children with hearing loss and has therefore commonly been implicated in studies analysing EF in paediatric CI users (Kronenberger et al., 2020; Pisoni et al., 2011). It involves an examiner reading aloud a series of digits at a rate of one item per second, and the child verbally repeating back the sequence in the same order. However, many other researchers have questioned whether the Digit Span Forward subtest truly examines verbal WM and instead propose that it is merely a measure of short-term verbal memory rather than verbal WM. This is because the test requires a subject to simply recall a sequence of digits in the order it was presented, rather than demanding any additional processing or manipulation of the stored information (Kidd, 2013; AuBuchon et al., 2019). Less controversy appears to surround the Digit Span Backward subtest of the WISC-V as a measure of verbal WM because it requires a child to repeat digits in a reverse sequence

(than was originally presented to them), hence requires manipulation of the stored verbal information prior to responding.

Both the Digit Span Forward and Digit Span Backward subtests are standardised on a normative paediatric sample aged over 6 years, thus are only validated for use in children above this age (Wechsler, 2014). These assessments are commonly used in research studies involving deaf children, in addition to others such as the Forward Memory subtest of the Leiter International Performance Scale-Revised (Leiter-R; Roid & Miller, 1997) and the Attention Sustained Total subtest of the Leiter-R (Roid & Miller, 1997). These latter tests evaluate visual short-term/working memory and IC respectively. Table 2.2 provides a description of these tests in addition to an overview of commonly described tasks for achieving behavioural measures of EF in early childhood in both NH and children with CIs.

Table 2.2: An overview of behavioural EF tasks available for early childhood

Task	EF Component	Description	Age	Reference(s)
Tongue task	IC	A child is asked to hold an edible object on their tongue without eating it for time intervals of 10, 20 and 30 seconds.	22 months +	Kochanska et al., (2010); Cuevas et al., (2014)
Crayon delay task	IC	A chid is presented with a box of crayons and a blank piece of paper. The experimenter instructs the child not to touch any of the items until he/she returns after leaving the room for a short period.	24 months +	Calkins et al., (1997); Morasch & Bell, (2011)
Mommy-Me task	WM & IC	A child is asked to remember two rules and exhibit inhibition control by performing a subdominant response. The child is instructed to say "mummy" when shown a picture of himself or herself and say "me" when shown a picture of the mother.	24 months +	Bell & Wolfe, (2007); Broomell et al., (2019); Cuevas et al., (2012)
Leiter-R attention sustained subtest	IC	A child is timed whilst they cross out target pictures i.e. animals from an array containing target and distractor pictures.	36 months +	Roid & Miller, (1997)
Leiter-R forward memory subtest	Visual STS/WM	An examiner points to a sequence of pictures of common objects, which the child must then reproduce by pointing to the same pictures in the same sequence.	36 months +	Roid & Miller, (1997)
Stroop-like Day-Night task	IC	A child is instructed to say "day" in response to the picture of a moon with some stars and "night" in response to picture of a sun.	36 months +	Gerstadt et al., (1994); Moriguchi et al., (2012)
Stroop-like Yes-No task	IC	A child is instructed to say "yes" when the experimenter shakes their head no and to say "no" when the experimenter nods their head yes.	36 months +	Bell & Wolfe, (2007)
Dimensional Change Card Sort (DCCS) task	CF	A child is asked to sort cards that have two dimensions such as colour and shape. During the pre-switch phase children are asked to sort the cards according to one dimension i.e. colour. During the post-switch phase children are asked to sort the cards according to the other dimension i.e. shape.	36 months + (Pre-switch phase) 48 months + (Post-switch phase)	Zelazo et al., (2006); Moriguchi et al., (2010); Moriguchi et al., (2012)
Go/NoGo task	IC	A child is asked to respond to targets by pressing a button (Go trials) and to avoid making a response to non-targets (No-Go trial).	48 months +	Smith et al., 2017; Mehnert et al., 2017
N-back task	WM	A child views black shapes (e.g. star, circle) presented in a white screen and are told to push the response button only if they see the same shape twice in a row.	48 months +	Smith et al., (2017); Mehnert et al., (2017)
Digit Span Forward and Digit Span Backward subtests of the WISC-V	Verbal STS/WM	The examiner presents a series of digits aloud, and the child must repeat them back in spoken format either in the same order (Digit Span Forward) or backwards order (Digit Span Backward).	6 Years +	Wechsler, (2014)

IC = Inhibition control, WM = Working memory, STS = Short-term memory, Leiter-R = Leiter International Performance Scale – Revised, WISC-V = Wechsler Intelligence Scale for Children ® – Fifth Edition.

2.4.4 Summary

Several researchers have designed or adapted innovative and effective behavioural measures of EF. In addition to those already described, there are a plethora of other EF tasks described in the literature that were unable to be covered in this chapter. However, little consensus or guidance is available on which behavioural EF tasks are clinically appropriate for a given chronological age range or developmental ability. Furthermore, no standards or parameters for appropriate behavioural performance are available. Measuring verbal WM may be of specific importance when examining the relationship between EF and language, particularly for CI users. However, controversy surrounds tests that are commonly accepted to assess verbal WM, with many researchers proposing that tests such as the Digit Span Forward subtest examine short-term memory only. Furthermore, tests deemed capable of analysing verbal WM are validated only in older children when a vast amount of language acquisition should theoretically have already occurred, in typically-developing children at least.

As highlighted in this literature review, solely relying on behavioural measures to clarify the relationship between EF and language development has its drawbacks. Direct, objective correlates of cortical function may facilitate further understanding of the variable language outcome in both NH children and deaf-implanted children. The relationship between cortical development and the emergence of EF is far from fully established, hence limits our understanding of

how deficits in EF arise. The use of neuroimaging techniques may help identify neural markers of aberrant EF development and processing. An initial and mandatory step in designing effective EF interventions is to understand the developmental mechanisms involved in its emergence, and of specific importance to CI users, how these processes differ in the auditory-deprived brain. If an association between behavioral EF and language development exists, then early identification of deficits in central EF processing via objective imaging techniques may allow for prompt intervention with more focused rehabilitation approaches.

2.5 EXAMINING NEURAL MECHANISMS OF EXECUTIVE FUNCTION IN THE NORMAL-HEARING AND DEAF-IMPLANTED CHILD

Established neuroimaging research supports a relationship between EF and the PFC. Multiple studies have demonstrated the PFC, specifically areas of the lateral prefrontal cortex (LPFC), to be significantly activated during EF tasks (Aron et al., 2014; Konishi et al., 1998; Laird et al., 2005; Monchi et al., 2001; Wager & Smith, 2003). Functional magnetic resonance imaging (fMRI) studies support the theory that regions of the LPFC are responsible for multiple EF processes in adulthood (Cohen et al., 1997; D'Esposito & Postle, 1999), and furthermore, in late childhood and adolescence (Casey et al., 2011; Crone et al., 2006; Nelson et al., 2000). Although the PFC is reported to follow a slower developmental course compared with other cortical regions (Fuster, 1993;

Huttenlocher & Dabholkar, 1997), evidence from neurophysiological and neuroimaging studies suggests that the PFC is also active during infancy. Whilst conducting this literature review, it became apparent that the definition of the functional and anatomical subdivisions of the LPFC varied amongst neuroimaging studies. However, Figure 2.4 illustrates the most concordant terminology for the various regions of the LPFC, which is adhered to throughout this thesis (Badre, 2008).

Figure removed

Figure 2.4: The major anatomical sub-divisions of the prefrontal cortex. Various regions of the lateral prefrontal cortex have been implicated in executive function processes. This diagram illustrates the sub-divisions of the lateral prefrontal cortex and their associated Brodmann areas. The ventrolateral prefrontal cortex (VLPFC) may also be referred to as the inferior frontal cortex/gyrus. For the purposes of the thesis, we adhere to the term VLPFC when referring to this brain region. Taken and adapted from Badre (2008).

It is likely that EF processing is not solely reliant on the PFC, since regions of the parietal cortex and subcortical areas have more recently been implicated in EF (Moriguchi et al., 2018). As discussed earlier in this chapter, evidence suggests that a congenital deafness leads to auditory areas becoming decoupled from higher-order prefrontal regions typically involved in cognition (Sharma et al., 2009). The examination of behavioural EF-evoked activation in superior temporal regions, in addition to an evaluation of neuronal connectivity between these auditory areas and those typically implicated in EF processing, may be vital to understanding why behavioural EF deficiencies arise more commonly in deaf-implanted children compared with their NH peers. However, when it comes to performing research in paediatric CI recipients, many of the

neuroimaging modalities have significant limitations for this cohort of children. Most studies examining cortical measures of EF have therefore, by default, occurred in the NH paediatric population. This highlights the fact that the neural mechanisms of EF development in the auditory-deprived infant brain, and the effect that rehabilitation with cochlear implantation has on such processes, are poorly understood.

2.5.1 The Limitations of Conventional Neuroimaging Techniques for Measuring Cortical Activation in Cochlear Implant Users

Functional neuroimaging enables the non-invasive measurement of neural activity within specific areas of the cerebral cortex and therefore has the potential to further our insight into the neurobiological factors that may determine outcomes following cochlear implantation (Saliba et al., 2016). Neuroimaging techniques can be divided into: 1) metabolic, which includes Positron Emission Tomography (PET) with labelled glucose; 2) haemodynamic, examples of which are PET with labelled water, fMRI and fNIRS, and; 3) electrophysiological, typically electroencephalography (EEG) and magnetoencephalography (MEG).

Functional Magnetic Resonance Imaging (fMRI) has become the gold standard for in-vivo imaging of the human brain. It is often the preferred neuroimaging modality of choice in adolescent and adult

subjects without a CI due to providing accurate information about the spatial resolution of brain activity. However, conventional CIs are not compatible with fMRI for many reasons. The internal magnet component of the CI device is not only a safety issue in an electromagnetic field, but also creates interference and artefact on the MR image. Whilst it is possible for CI users to safely undergo MRI scanning at low-power 1.5 Tesla if the CIs devices are binded with gauze material, large image artefact may still be problematic (Crane et al., 2010). Further limitations include the potential requirement for either sedation or general anaesthesia (GA) in younger children to eliminate movement artefact, in addition to the significant amount of background noise associated with this technique.

Positron Emission Tomography (PET) is a nuclear functional imaging technique that offers the advantage of being compatible with CIs, providing good spatial resolution and being relatively acoustically quiet. Several studies have reported the success of PET imaging for the evaluation of language processing in CI recipients (Aggarwal & Green, 2012; Giraud et al., 2001; Saliba et al., 2016). However, major disadvantages of this technique include high financial cost and the lack of ability to perform numerous and serial scans due to the associated exposure of research subjects to ethically questionable radioisotopes.

Electroencephalography (EEG) and MEG are both safe techniques and therefore lend themselves perfectly to multiple and repeated testing. These modalities directly measure the electrophysiological response of neural activation with excellent temporal resolution (Luck, 2005). EEG is able to tolerate subtle movements making it suitable for use in young children and infants (Saliba et al., 2016), hence it has been utilised in numerous studies evaluating EF in NH infants. However, limitations of EEG and MEG include relatively poor spatial resolution in comparison with techniques such as fMRI (Burle et al., 2015), interference of the electrical components of the implant with imaging equipment (that creates recording artefacts) and the requirement for magnetically shielded rooms with MEG use.

2.5.2 Principles of Functional Near-Infrared Spectroscopy

Functional near-infrared spectroscopy (fNIRS) is a non-invasive optical technique that is able to measure haemodynamic responses to neuronal activation via the use of near-infrared light (Boas et al., 2014). Specifically, fNIRS is based on the principle of neurovascular coupling whereby an increase in cortical activation, and the subsequent increased oxygen demand by the neuronal cells, stimulate an increase in local cerebral blood flow (Villringer & Chance, 1997). Like the blood oxygenated level-dependent (BOLD) signal of fMRI, fNIRS measures stimulus-evoked changes in levels of oxygenated haemoglobin (HbO) and deoxygenated haemoglobin (HbR) that result from neuronal activation rather than directly measuring cortical activity (Figure 2.5).

To measure changes in HbO and HbR, low-power near-infrared light is directed through the scalp and into the cortex via fibre-optic bundles called optodes (see Figure 2.6). Continuous wave fNIRS systems emit two frequencies of near-infrared light via emitter probes that are coupled with the absorption of HbO and HbR (Lloyd-Fox et al., 2010). Returning light is detected by detector probes within the optode array. The amount of returning near-infrared light provides a measure of how much light has been absorbed by the chromophores at a specific anatomical region located between each emitter-detector pair, referred to as a measurement channel. The quantities of HbO and HbR can then subsequently be derived. However, scattering of light within the cerebral cortex also attenuates emitted light. Hence, when a change in chromophore concentration (△HbO or △HbR) is calculated from raw measures of optical density, the modified Beer-Lambert law is applied to correct for these light scattering effects (Huppert et al., 2009). Changes in blood flow within the scalp are also sensitively detected by fNIRS, where systemic signals such as heart rate are also present

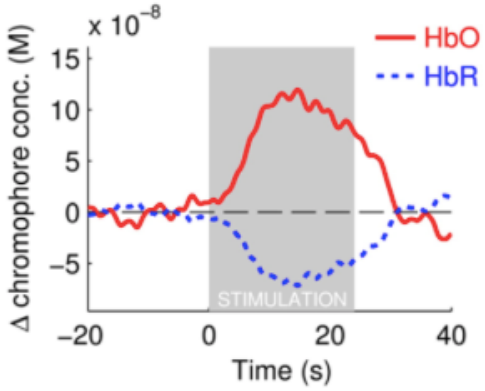


Figure 2.5: A typical response to brain activation measured with fNIRS. Following the onset of a stimulus, an increase in oxygenated haemoglobin (HbO) is

observed due to increased neuronal activation. A smaller but relative decrease in deoxygenated haemoglobin (HbR) also occurs. Taken from Lawler et al. (2015).



Figure 2.6: A photograph of a fNIRS optode array. Emitter optodes emit near-infrared light and detector optodes measure the amount of returning light. This is used to measure cortical activation bilaterally.

(Boas et al., 2004). Hence, systemic vascular changes have the potential to be falsely attributed to a functional haemodynamic response measured over the cerebral cortex. However, to attenuate this contamination effect, the fNIRS signal can be separated into estimates of the systemic and functional response which can be effective for removing physiological noise and extracting the functional component from the fNIRS signal (Yamada et al., 2012).

When the temporo-spatial characteristics of fNIRS are compared with other neuroimaging methods, there are both advantages and disadvantages. For example when compared with EEG, fNIRS is associated with lower temporal resolution due to the relatively slow nature of the haemodynamic response, yet offers better spatial localisation (Emberson et al., 2017). Conversely, fNIRS is able to

acquire measurements of the haemodynamic response more rapidly than fMRI, hence has higher temporal resolution than this technique (Huppert et al., 2006). The extent of light penetration into the cortex (Toronov et al., 2007), in addition to the absorption and scattering of light by the skull and cerebrospinal fluid (Okada & Delpy, 2003), limits the spatial resolution of fNIRS which is less favourable than fMRI. Resolution in the depth axis is limited due to typically small source-detector separations in optode arrays (Boas et al., 2004) meaning that fNIRS cannot provide imaging of underlying brain anatomy (such as subcortical structures). Whilst wider source-detector separations provide greater spatial resolution in the depth axis, they compromise resolution in the brain in the axis parallel to the scalp. Therefore, it is currently not possible to localise the anatomical origin of fNIRS detected cortical activations with precision. However, the implementation of 3D digitizers and associated spatial-registration software allow for more accurate estimation of the anatomical origin of cortical activation in addition to aiding the reduction in variability across subjects (Singh et al., 2005; Tsuzuki et al., 2012).

2.5.3 The Application of Functional Near-Infrared Spectroscopy to Executive Function Neurodevelopmental Research

In addition to its modest and compromising temporo-spatial characteristics, fNIRS offers many other advantages, thus is gaining ever increasing popularity in the field of infant EF

neurodevelopmental research. Firstly, distinct from fMRI, it avoids the need for a child to lie alone within a scanning machine environment. Infants are therefore able to remain awake and engage in behavioural tasks whilst sitting comfortably with a parent or guardian. Secondly, fNIRS is a safe, non-invasive technique that avoids the administration of radioactive substances, sedation and/or GA, hence is suitable for longitudinal research and clinical studies. Furthermore, this modality is less sensitive to head movements than other neuroimaging methods (Aslin & Mehler, 2005), is acoustically quiet and portable and suitable for use in both adult (Anderson et al., 2017) and paediatric (Sevy et al., 2010) CI recipients. Pertinent to this thesis, and as discussed in the upcoming sections, fNIRS has been successfully used in numerous studies examining both resting-state cortical connectivity and cortical connectivity on behavioural EF-evoked brain activation in infants and children whilst they perform tasks encompassing all three core components of EF: 1) IC (Mehnert et al., 2013); 2) WM (Buss et al., 2014; Perlman et al., 2016), and; 3) CF (Moriguchi & Hiraki, 2011). However, paediatric fNIRS studies that have longitudinally examined cortical correlates of EF are limited in number. Furthermore, it is apparent from this literature review that fNIRS is yet to be specifically applied to children with CIs for the purpose of examining the neural basis of EF development in the auditory-deprived brain.

2.5.4 Established Neuroimaging Studies of Executive Function in The Normal-Hearing Child

2.5.4.1 The Neural Mechanisms of Executive Function Development During Infancy

The vast amount of research examining the cortical correlates of behavioural EF in the first year of life has employed EEG, most likely because this imaging modality is relatively well tolerated in infancy (Lloyd-Fox et al., 2010). This technique measures scalp electrical activity that is considered to reflect underlying cortical function. Research studies have concentrated on investigating EEG power, which measures the size and frequency of neuronal signals, and EEG coherence which calculates functional connectivity between two electrodes during an EF task (Bell & Cuevas, 2012; Broomell et al., 2019). Data from infant EEG studies has revealed EF task-related changes in both frontal EEG power (Cuevas & Bell, 2011) and coherence (Bell & Wolfe, 2007). In terms of the A-not-B task, which analyses behavioural WM and IC, infants exhibit increased frontal coherence when responding to an added inhibitory demand, such as when a reversal B-trial is performed rather than an A-trial (Cuevas, Bell, et al., 2012). Higher frontal power and coherence has also been observed in infants when they respond correctly rather than incorrectly to trials on the A-not-B task (Bell, 2002; Cuevas, Raj, et al., 2012). Furthermore, frontal EEG power measured in infancy has been shown to predict later A-not-B task performance (Cuevas, Bell, et al., 2012). Many of these EEG studies have identified EF-evoked increased power in the DLPFC specifically (Bell, 2001, 2012;

Cuevas, Bell, et al., 2012), hence this region is considered to play a key role in WM processes (Diamond, 2002). Evidence from EEG studies also suggests a role for the parietal cortex in infant EF processes. Infants who have higher performance scores on the A-not-B task exhibit task-related increases in both frontal and parietal power in addition to increased coherence between these two brain regions (Bell, 2001, 2012). Furthermore, the latter measure of connectivity is able to predict later EF performance (Bell, 2012).

Although fMRI has been used to examine EF neurodevelopmental mechanisms in infants (Madhyastha et al., 2018), studies implementing this modality are extremely limited due to the poor tolerance of this technique by younger children and toddlers (Fiske & Holmboe, 2019). Conversely, many researchers have employed fNIRS imaging in infant EF studies since it allows subjects to perform motor-based EF tasks whilst awake and in an unconfined and more comfortable environment. Baird et al. (2002) used fNIRS to examine cortical activation whilst infants performed a variation of the A-not-B task and found that participants recruited the DLPFC when holding the location of objects in WM (Baird et al., 2002). Other brain regions have also been implicated in infant WM on fNIRS imaging. Wilcox and Biondi (2015) found that infants activated both the posterior temporal cortex and occipital cortex during a visual WM task. However, fNIRS responses in the posterior temporal cortex decreased from 7 months of age onwards and were negligible by 10 to 13 months, whereas fNIRS activation in the

occipital cortex was unaffected by increasing age. The aforementioned led the authors to propose that such findings reflect the functional specialisation of visual WM processes throughout infancy (Wilcox & Biondi, 2015).

Evidence from neuroimaging studies therefore suggests that prefrontal areas, notably the DLPFC, are fundamental to infant EF. Other brain regions such as the posterior temporal cortex and parietal cortex may also play a role. However, further evidence is required to clarify whether parietal areas are implicated in early EF development since parietal lesions do not significantly affect A-not-B performance in animal infant models (Diamond & Goldman-Rakic, 1989).

2.5.4.2 The Neural Mechanisms of Executive Function Development During Early Childhood

Evidence for a role of the PFC in EF processes beyond infancy is provided by numerous neuroimaging studies. With respect to fNIRS, Perlman et al. (2016) administered a visuospatial WM task to 3 to 7 year old children and found increased task-induced activation of the DLPFC and ventrolateral prefrontal cortex (VLPFC) bilaterally, an effect that increased with age (Perlman et al., 2016). Interestingly, Smith et al. (2017) assessed WM using the non-spatial visual N-back task in 4 to 10 year old children and reported increased fNIRS responses in bilateral orbitofrontal regions. This task-induced activation was reported to increase with age and measures of

behavioural task performance (Smith et al., 2017). Involvement of the parietal lobe in early childhood WM development is supported by an fNIRS study by Buss et al. (2014) who found increased bilateral activation in both the DLPFC and parietal cortex of 3 to 4 year old children during a visual WM task. In parietal areas specifically, the response was more robust in 4 year old compared with 3 year old children (Buss et al., 2014).

Increasing age allows for improved tolerance of fMRI, hence EF research studies utilising this image technique in children are not too infrequent. Increased activation of the DLPFC measured with fMRI has been shown to correlate with behavioural performance on visual WM tasks (Ullman et al., 2014), a finding consistent with the fNIRS study by Perlman et al. (2016). However, this observed DLPFC fMRI activation was not predictive of future WM performance. Instead, activation within other brain regions including the basal ganglia and thalamus was able to predict future behavioural WM ability (Ullman et al., 2014). Conversely, a fMRI study by Crone et al. (2006) reported that in contrast to older children and adults, 8 to 12 year old children failed to recruit the right DLPFC and bilateral superior parietal cortex (Crone et al., 2006) whilst all children and adults equally recruited the VLPFC bilaterally during a visual WM task. As reflected in the evidence presented so far, most neuroimaging studies have used visual tasks to assess neural correlates of WM. However, Vogan et al. (2018) combined fMRI and a verbal WM task in typically-developing children and children with

ASD, both groups aged between 9 and 16 years. Typically-developing children showed significantly increased activation in the DLPFC bilaterally (more extensive in the right hemisphere), superior parietal regions bilaterally and the left VLPFC. Interestingly, the ASD group who are at increased risk of EF deficits showed minimal recruitment of the lateral prefrontal and parietal regions during the verbal WM task (Vogan et al., 2018).

With respect to IC, the Go/NoGo task has been extensively used to assess this element of EF. Adult fMRI studies employing this EF task have shown task-induced activation of the right VLPFC (Aron et al., 2014). Interestingly, a longitudinal fMRI study by Durston et al. (2006) identified that in children aged between 9 and 11 years at recruitment, IC-induced activation within the right VLPFC increased with age whilst activation within other prefrontal areas such as the DLPFC decreased. Evidence for right VLPFC activation on IC tasks is also available from fNIRS studies. Moriguchi & Shinohara (2019) found right sided VLPFC activation during a reward IC task in 3 to 4 year old children (Moriguchi & Shinohara, 2019). Mehnert et al. (2013) also discovered that children aged 4 to 6 years demonstrate a high level of fNIRS activation in right lateral prefrontal and right parietal regions during the Go/NoGo task. However, task-induced activation was universally high during both the Go and NoGo trials in children, who in comparison with adults, displayed reduced IC-induced activation in both lateral prefrontal and parietal areas (Mehnert et al., 2013). Interestingly, results from neuroimaging

studies have often provided contradictory evidence in terms of IC-evoked cortical activation. Whilst some paediatric fMRI studies, as already described above, demonstrate increasing IC task-induced right-sided VLPFC activation with age (Durston et al., 2006), others report this relationship to occur specifically within the left VLPFC (Tamm et al., 2002).

With respect to cognitive flexibility (CF), results from neuroimaging studies remain relatively consistent across modalities in terms of neural mechanisms of EF in early childhood. A fMRI study involving adults and school-age children revealed activation of the DLPFC, VLPFC and superior parietal cortex during a DCCS task (Morton et al., 2009). Interestingly, children tended to preferentially recruit right frontal regions over other regions, whereas adults had superior levels of activation within the left superior parietal cortex and right thalamus (Morton et al., 2009). Similarly, in a longitudinal fNIRS study, Moriguchi & Hiraki (2011) examined the development of prefrontal activation whilst children performed the DCCS task at 3 years of age (time 1) and subsequently 4 years of age (time 2). In terms of behavioural results, children who made errors at time 1 (perseverate group) improved their performance significantly and children who did not commit errors at time 1 also performed correctly at time 2 (pass group). In terms of fNIRS responses, children in the pass group showed significant right VLPFC recruitment during the pre-switch and post-switch phases at time 1 and time 2. However, children in the perseverate group showed no

significant activation in either VLPFC during the pre-switch and post-switch phases at time 1, whereas at time 2 they showed significant activation in the left VLPFC during both phases. This led the authors to suggest that right lateral frontal areas may be relatively dominant in DCCS tasks, whilst left lateral frontal areas may compensate for right-sided activations in this region (Moriguchi & Hiraki, 2011). Further supportive evidence for this theory comes from a fNIRS study involving children with ASD (Yasumura et al., 2012). Children with ASD had less favourable performance on an advanced version of the DCCS task and exhibited lower right VLPFC activation compared with typically-developing children.

Overall, the above reviewed literature on the cortical correlates of typically-developing behavioural EF in early childhood supports a role for lateral prefrontal and parietal regions, the latter area perhaps becoming more substantial with increasing age. Like infant studies, the contribution of superior temporal regions to EF processing has been less extensively investigated. Although the neuroimaging evidence is relatively consistent, there are discrepancies. For example, with respect to IC neural mechanisms, some studies report the right VLPFC to be of developmental significance, whereas others suggest the left VLPFC to have a more important role in this domain.

2.5.5 Established Neuroimaging Studies of Executive Function in The Deaf Child

All evidence relating to the neural mechanisms of EF discussed so far in this chapter has involved the NH paediatric population. The conduct of this literature review failed to identify any neuroimaging studies that related to behavioural EF task-induced cortical activation in children with a severe-to-profound hearing loss, thus exposing the rationale for such an examination within this thesis and elsewhere.

2.5.6 Established Neuroimaging Studies of Cortical Connectivity

As previously alluded to, cortical connectivity studies have complemented neuroimaging research by revealing neural mechanisms fundamental to cognitive processes and their behavioural manifestations. The resting-state refers to the spontaneous brain activity measured during a period of quiet alertness and attention in the absence of overt cognitive information processing by a subject. Resting-state brain activity is being increasingly used to evaluate the development of connectivity within and between specific cortical regions. Measures of resting-state neural connectivity between frontal and other cortical regions have already been shown to predict later behavioural performance on both EF (Broomell et al., 2019) and language assessments (Mundy et al., 2003). Furthermore, as discussed earlier in this chapter, infants who have higher performance on EF tasks exhibit task-

related increases in connectivity between frontal and parietal regions (Bell, 2001, 2012). However, this evidence has been provided by EEG studies involving NH infants. Therefore, in the following sections we explore the literature on cortical connectivity studies employing various other imaging modalities that have been conducted in NH and deaf subjects.

2.5.6.1 Functional versus Directed Cortical Connectivity

It is apparent from the literature that most cortical connectivity studies have employed functional connectivity (FC) analysis. This method of analysing neuronal connections defines temporal correlations between spatially remote neurophysiological events. Hence, FC is a statistical association of neuronal activity time courses across distinct brain regions (Friston, 2011). Since FC describes statistical dependencies, it reports no more than which brain region displays a similar neural fluctuation pattern to another. A more informative way to measure cortical connectivity may be provided by directed connectivity (DC) metrics that detail the causal influence that one neuronal system exerts over another. Specific techniques for assessing DC include Granger Causality (GC), (Granger, 1969) dynamic causal modelling (DCM) (Friston et al., 2003) and phase transfer entropy (PTE) (Lobier et al., 2014). However, GC is reportedly sensitive to signal noise (Nalatore et al., 2007) and DCM requires strong assumptions on underlying neuronal mechanisms. Lobier et al. (2014) claim that PTE can overcome the

limitations of GC and DCM and is thus a more suitable technique for large-scale evaluations of DC.

2.5.6.2 Executive Function Neuroimaging Studies Utilising Cortical Connectivity Analysis

Evidence from neuroimaging studies in typically-developing children utilising FC analysis suggests that improving behavioural EF task performance is likely related to evolving cortical connectivity between brain regions implicated in EF processing. When compared with adults, children exhibit weaker fMRI detected FC between the lateral PFC and inferior parietal cortex during a DCCS task (Ezekiel et al., 2013). Paediatric fNIRS studies have also demonstrated different patterns of cortical connectivity on EF task-evoked brain activation between children and adults. Functional connectivity analyses in the fNIRS study by Mehnert et al. (2013) revealed 4 to 6 year old children have stronger short-range connectivity within frontal brain regions and weaker long-range connectivity between frontal and parietal areas, compared with adults. Conversely, adults displayed stronger long-range FC between bilateral PFC and the right parietal cortex, suggesting EF development is associated with maturation of the fronto-parietal network (Mehnert et al., 2013). However, such connectivity on EF-task evoked activation has been shown to increase throughout early childhood with individuals aged 4.5 years exhibiting stronger FC in the fronto-parietal network than those aged 3 years (Buss & Spencer, 2014). Evidence from fMRI studies also highlights the importance of cortical connectivity

between frontal areas and deeper regions of the cortex, such as the striatum, in the successful evolution of behavioural EF (Rubia et al., 2006). However, fNIRS is unable to detect activation from such subcortical regions due to the limited depth penetration of near-infrared light.

With respect to children with severe-to-profound SNHL, a literature reviewed failed to identify any neuroimaging studies that have specifically examined connectivity on EF-task evoked brain activation. Although extremely limited in quantity, there are studies that have investigated resting-state FC in infants and children with severe-to-profound SNHL. Interestingly, fMRI studies consistently report increased resting-state FC within and between auditory regions (primary auditory cortex and superior temporal cortex) in deaf, non-implanted infants and children compared with NH peers (Tibbetts et al., 2011; S. Wang et al., 2019; Xia et al., 2017). Tibbetts et al. (2011) also described increased FC within the left parietal cortex, an area linked with WM processes, of 7 to 17 year old children with a severe unilateral SNHL. A suggested explanation for the observed increase in FC within auditory regions of children with hearing loss is a compensatory activation and neuronal reorganisation in response to a lack of auditory stimulation (S. Wang et al., 2019). In terms of increased FC in WM processing regions, a greater reliance on silent rehearsal for WM tasks in deaf children compared with NH controls is a hypothesised reason for this observation (Tibbetts et al., 2011). Although a PET study by

Lee et al. (2007) was not designed to examine FC per se, it did examine resting-state cortical activity in children aged between 1 and 11 years old with a severe-to-profound deafness prior to cochlear implantation. Children with good speech understanding three years post-implantation were found to have enhanced metabolic activity in the left PFC compared with those who had poor speech perception (Lee et al., 2007). This finding may suggest that increased resting-state cortical activity in higher-order EF processing regions facilitates improved CI language outcomes, however limited studies in this cohort of children make it impossible to draw any definitive conclusions. The technique of fNIRS is able to overcome many of the limitations of conventional imaging modalities, hence has already been used to investigate resting-state functional connectivity in CI users (McKay et al., 2016). Although evidence is currently limited to the adult population, it highlights the promise for fNIRS to investigate cortical connectivity and activation in paediatric CI recipients. Mckay et al. (2016) performed FC analysis on resting-state data acquired from one NH adult listener and one adult CI user and reported a lack of diffuse inter-hemispheric connectivity in the latter subject.

Directed connectivity analysis has yet to be utilised in EF neurodevelopmental research specifically, however it has been employed in both fMRI and fNIRS neuroimaging studies. For example, DCM has recently been demonstrated as reliable for measuring infant cortical connectivity by Bulgarelli et al. (2018) who

simultaneously recorded fMRI and fNIRS data from a sleeping infant aged 6 months. The infant was presented with auditory stimuli in a block design and high correspondence was found between fMRI and fNIRS directed connectivity data within and between inferior frontal, superior temporal and parietal regions (Bulgarelli et al., 2018). Phase Transfer Entropy (PTE) has also been successfully implemented in the analysis of task-induced directed connectivity during an adult fNIRS motor fatiguing handgrip task (Urquhart et al., 2020).

2.5.7 Summary

Although cortical activation within and connectivity between prefrontal, parietal and temporal brain regions appear to be implicated in EF neurodevelopmental mechanisms, further neuroimaging studies are required to investigate neural correlates of EF processing, especially in deaf children. Longitudinal studies would not only enable an evaluation of how EF neural mechanisms change with time and cochlear implantation, but also whether such factors can predict later language outcome in both NH children and children with CIs. Well-established neuroimaging modalities including fMRI, EEG, MEG and PET are limited in their application to paediatric studies due to either their restricted compatibility with CI devices or their adverse safety profile. The technique of fNIRS overcomes these hurdles via its resistance to CI-generated artefacts (Sevy et al., 2010) and by being well-suited to longitudinal adult and paediatric studies (Lawler et al., 2015; Saliba et al., 2016; Sevy

et al., 2010). There is an exciting amount of studies that have utilised fNIRS to study cortical activation and connectivity patterns during both the resting- and behavioural EF-task induced state. Although most of this research has been performed in typically-developing infants and children, fNIRS offers a powerful tool to examine the neural mechanisms of EF development in children with severe-to-profound SNHL, both pre- and post-cochlear implantation.

2.6 AIMS OF THE THESIS

The premise of this review is that paediatric CI users' auditory speech perception abilities remain highly variable and unpredictable. This chapter has reviewed evidence of the influence that certain characteristics such as demographic, clinical and socioeconomic factors can have in determining the amount of benefit derived from cochlear implantation. The current evidence suggests that CI outcome in the paediatric population cannot be accurately predicted solely on this routinely available data. The literature review presented a growing body of evidence that suggested executive functioning could be an important factor in understanding how much benefit individual children will receive from CI insertion. The overall goal of this work is to understand the development of behavioural and cortical correlates of EF in both NH children and children with CIs, and whether such measures can help explain the observed variability in language outcome amongst paediatric CI users.

To date, methodological challenges have precluded the longitudinal examination of cortical function in children. More recently, the promising application of fNIRS in studying cortical activation and connectivity in children with and without CIs has been recognised. Therefore, in conjunction with behavioural measures, fNIRS offers a powerful tool to elucidate the relationship between cortical correlates of EF and future language outcome. Despite this, the author is unaware of any such empirical examinations in deaf-implanted children within the literature. Resultantly, the specific aims of this thesis are:

i. To investigate the development of behavioural EF in NH children and in deaf children with CIs.
ii. To examine the relationship between behavioural EF and language performance in NH children and paediatric CI users.
iii. Use fNIRS imaging to examine the cortical correlates of behavioural EF in NH children and children with CIs, and whether these fNIRS correlates are associated with language outcome.
iv. To evaluate the suitability of fNIRS for acquiring repeated measures of behavioural EF task-evoked cortical activation, in addition to repeated measures of fronto-temporal connectivity, from the prefrontal and superior temporal brain regions of NH children and children with CIs.

v. If iii) and iv) prove successful, to examine how behavioural EF task-evoked cortical activation and correlates of fronto-temporal connectivity change in NH children and children with a severe-to-profound SNHL, not only over time, but also following cochlear implantation.

vi. To investigate whether fNIRS correlates of behavioural EF and fronto-temporal connectivity can predict later behavioural EF and language performance in both NH children and children with CIs.

2.7 THE IMPACT OF COVID-19 ON NATIONAL HEALTH SERVICE COCHLEAR IMPLANT PROGRAMMES

2.7.1 Interruptions to Cochlear Implant Surgery

In January 2020, The World Health Organisation declared the novel coronavirus (SARS-CoV-2) outbreak an international public health emergency (Zarocostas, 2020). The delivery of all aspects of healthcare within the NHS subsequently underwent scrutinous reassessment and reorganisation (Willan et al., 2020). National Health Service CI programmes throughout the UK were naturally affected, and understandably, in March 2020 there was a temporary pause in not only face-to-face outpatient clinics, but also CI surgeries at The Nottingham Auditory Implant Program (NAIP) based at NUH NHS Trust, and all other CI programmes affiliated with this thesis.

In response, HCWs across all specialities strived to resume non-COVID-19 related services on the premise of a safe environment for all patients and staff. The Royal College of Surgeons (RCS) published a clinical guide to surgical prioritisation during the COVID-19 pandemic (RCS, 2020), and with respect to cochlear implantation, the most pressing cases were identified as: 1) pre-lingually deaf children to avoid significant speech and language delay; 2) deafness following meningitis, and; 3) device failure. When indicated for the risk of ossification post-meningitis and device failure, these RCS guidelines stated surgical implantation should occur within a month of diagnosis.

However, early in the first wave of the pandemic, otolaryngologists imminently faced a dilemma as countries including China and Italy reported high rates of infection within this group of specialists (Patel Z, 2020; Vukkadala et al., 2020; Xu et al., 2020). Specific to otology surgery, this high transmission rate may be explained by the fact that the nasopharynx, which is directly connected to the ear by the eustachian tube has been shown to contain a significant load of the SARS-CoV-2 virus (Kesser, 2020). Furthermore, the COVID-19 pathogen has been isolated from the middle ear and mastoid of human post-mortem dissections (Frazier et al., 2020). For this reason, middle ear and mastoid procedures are considered aerosol generating procedures (AGPs) (Canadian Society of Otolaryngology-Head & Neck Surgery, 2020; Thamboo et al., 2020). Although SARS-CoV-2 is transmitted by fluid droplets (10 – 100 μm) it has

been suggested, albeit subject to controversy (Ningthoujam, 2020), that the virus can also spread over longer distances by aerosols (particles < 10 μm) (Asadi et al., 2020). Since mastoidectomy, a vital surgical step in cochlear implantation, is considered an AGP (Thamboo et al., 2020) there is a hypothesised risk of COVID-19 transmission from an infected patient to theatre staff during CI surgery (ENT UK, 2020). Cochlear implantation and other mastoid surgery were therefore halted until appropriate PPE and other infection prevention IPC measures, that were considered vital for reducing viral transmission to HCWs during such procedures, were safely implemented.

2.7.2 Recommended Personal Protective Equipment for Cochlear Implant Surgery and the Subsequent Resumption of Services

To facilitate the safe recommencement of cochlear implantation in the COVID-19 era, a team of internationally recognised experts was formed, that consisted of surgeons from NAIP, academics from The National Institute of Health Research (NIHR) Nottingham Hearing Biomedical Research Centre (NHBRC), scientists and engineers from The University of Nottingham and anaesthetic and operating theatre staff from NUH NHS Trust. The intention was to develop a preclinical model of CI surgery that would enable an assessment of the risk of COVID-19 transmission from an infected patient to HCWs, and to then subsequently evaluate potential PPE and IPC solutions that may mitigate this transmission risk. Although the specific aim was

to achieve a resumption of cochlear implantation at NAIP, it was hypothesised that the findings may also facilitate the safe restart of CI and other mastoid surgery at other auditory implant programmes, both within the UK and worldwide.

The outcome of the preclinical study led to the development of recommendations on the PPE and IPC measures required for CI and other mastoid surgery during the COVID-19 era. These recommendations were subsequently implemented by NUH NHS Trust, and hence led to the resumption of CI surgery at NAIP in May 2020. To monitor the efficacy and safety of these procedures, the first ten CI/other mastoid surgeries following the implementation of the recommendations at NUH NHS Trust were individually evaluated using a systematic risk-based approach (R. M. Jones et al., 2020). The use of a novel commercially designed drape tent, that was hypothesised to have advantages over other established tent designs, was also assessed during these ten clinical level evaluations.

2.8 THE IMPACT OF COVID-19 ON THIS THESIS

2.8.1 Cross-Sectional and Longitudinal fNIRS Experiments

The COVID-19 pandemic paused face-to-face research activity and, in turn, participant recruitment and testing sessions for nine months from March through to December 2020. This pause occurred seven months after commencing recruitment to the longitudinal study, hence had a severe impact on the timing and number of research

sessions that were originally scheduled to take part during this experiment. Despite UK government guidance allowing the restart of essential face-to-face research activity in December 2020, regional and national lockdowns intermittently continued in the UK, hence recruitment to both the cross-sectional and longitudinal experiments continued to be adversely affected. Participant attendance at scheduled longitudinal research sessions also suffered. Low recruitment and high attrition rates were especially problematic in children with CIs since a substantial number of these participants lived outside of Nottinghamshire, hence travelling to the primary research site at The NIHR NHBRC was at times problematic due to the numerous travel restrictions in place throughout the various UK lockdowns.

2.8.2 Implementation of Parent-Reported Measures of Behavioural Executive Function Experiment

During the pause in face-to-face research activity, the relationship between EF and language performance continued to be explored through a newly implemented behavioural cross-sectional experiment. During this study, evidence-based tools were utilised to acquire parent-reported measures of EF and language ability. The measures employed were the Behavior Rating Inventory of Executive Function (BRIEF) (Gioia et al., 2003, 2015) and Children's Communication Checklist (CCC-2) (Bishop, 2003) as described in the following chapter, which outlines the methodology of this thesis.

3. EXPERIMENT DESIGNS AND METHODOLOGY

3.1 INTRODUCTION

This chapter describes the design and methodology of both a cross-sectional and longitudinal study performed in a group of children with severe-to-profound deafness, and in a separate group of NH children. In line with the overall aims of this thesis, both these studies were designed to examine the relationship between EF and language performance in both groups of children as they develop from infancy through to early childhood. Specifically, to understand the cortical mechanisms underlying behavioural EF in both the NH and auditory-deprived brain, fNIRS was used to measure cortical activation to an age-appropriate behavioural EF task from prefrontal and superior temporal brain regions. In terms of the severe-to-profound hearing loss group, the cross-sectional study involved children already implanted with bilateral CIs and the longitudinal study aimed to examine children both pre- and post- bilateral cochlear implantation. As cortical connectivity patterns in infancy have been shown to predict later cognitive ability (Deniz Can et al., 2013), fNIRS was also to measure resting-state cortical connectivity and cortical connectivity on behavioural EF task-evoked brain activation between prefrontal and superior temporal regions.

As described in section 2.8, the unprecedented COVID-19 pandemic caused a prolonged suspension of not only face-to-face research appointments, but also CI surgeries at all auditory implant

programmes recruiting participants to this thesis. Hence, COVID-19 had a substantial adverse impact on recruitment to both fNIRS experiments and furthermore interfered with the timing of testing session intervals in the longitudinal study. However, the resumption of CI surgery at the primary research site (NUH NHS Trust) was facilitated by both preclinical and clinical PPE studies that formed part of this thesis. Furthermore, whilst face-to-face sessions were paused, the investigation into the relationship between EF and language ability continued via implementation of the cross-sectional behavioural study in which parent-reported measures of EF and language performance were acquired. The details of these studies are also discussed in this chapter.

3.2 ETHICAL APPROVAL

All studies described in this thesis were approved by the Health and Social Care Research Ethics Committee A (HSC RECA) (REC reference:19/NI/0121) and sponsored by NUH NHS Trust (Research & Innovation reference: 19ET008). For the cross-sectional, longitudinal and parent-reported measures experiments a parent/guardian of each child participant gave written informed consent before taking part. Participants were recruited into the various studies between July 2019 and January 2021, with data collection conducted between July 2019 and April 2021. With respect to the PPE for CI surgery experiment, all participants taking part also gave written informed consent.

3.3 CROSS-SECTIONAL fNIRS EXPERIMENT

3.3.1 Participants

A group of severe-to-profoundly deaf paediatric CI recipients and a group of hearing children were recruited to this experiment. Common inclusion criteria across both groups were:

1) Native English speakers
2) Normal or corrected-to-normal vision
3) Aged between 4 years and 6 years and 11 months
4) Able to talk in simple sentences

Any known cognitive, motor, or language disorder (for example specific language disorder) were defined as exclusion criteria. Children in this age range were recruited because when combined with participants in the longitudinal experiment, language development (and its association with EF) could be assessed in children as they progress from 6 months old when expressive skills typically consist of babbling, through to 6 years of age when children are typically expected to easily and clearly communicate (Greydanus et al., 2008).

3.3.1.1 Normal-Hearing Children

Eighteen children with no known hearing problems were recruited. The group comprised eleven males and seven females with a mean age of 5.3 years (range 4.0 to 6.8 years, standard deviation (SD) = 0.8 years). Hearing subjects were recruited with the aim of further investigating the relationship between EF and language in typically-

developing children, and not for the purpose of performing quantitative statistical between group comparisons with CI participants. Where direct comparisons are made between the cross-sectional NH and CI participants in upcoming chapters, this is on a qualitative and descriptive case study type basis. Participants were recruited via the NIHR NHBRC's participant database, social media platforms, magazine advertisements and word-of-mouth by recruited participants.

Children were recruited into this group if their parent/guardian declared there were no known problems with or concerns about their hearing. Throughout this thesis, children in this group are referred to as normal-hearing (NH).

3.3.1.2 Children with Cochlear Implants

Two severe-to-profoundly deaf paediatric bilateral CI recipients were primarily recruited via the four NHS auditory implant programs affiliated with the study. Both participants were male, one aged 4.3 years and the other 6.6 years. The recruiting auditory implant programs included NAIP (located at the research site) and the following collaborating Participant Identification Centres (PICs): 1) Manchester Cochlear Implant Programme; 2) Midlands Hearing Implant Programme, and; 3) St George's Hospital Cochlear Implant Programme. The study was also advertised via other programmes such as The University of Southampton Auditory Implant Service and groups and societies that included the Cochlear Implanted

Children's Support (CICS) Group and the National Deaf Children's Society.

Relevant information regarding participants' clinical history of deafness was gathered from the relevant auditory implant programme's clinical records. A structural inner ear abnormality on pre-implantation computed tomography (CT) and/or MRI imaging was defined as an additional exclusion criterion.

3.3.1.3 Determining Sample Size

Children with CIs represent a novel population in terms of the use of fNIRS, hence there is a lack of data to inform a formal power calculation for this cohort of patients. However, Blasi et al. (2014) revealed a total of 13 typically-developing infants to be an adequate sample size for achieving high test-retest reliability when using fNIRS at the group level to repeatedly measure responses to auditory stimuli (Blasi et al., 2014). As discussed in Lloyd-Fox et al. (2010) often between 12.5 - 40% of data is removed from final analyses in fNIRS research due to movement artefacts, insufficient attention to stimuli and participant discomfort (Lloyd-Fox et al., 2010). This usually refers to removal of a single fNIRS channel and not removal of a full trial. However, to be conservative, for the purposes of this thesis a potential 40% participant removal rate due to incomplete or insufficient data was factored for. Originally, a recruitment target of 19 participants for each of the CI and NH group of children was set, albeit without the foresight of the

impending COVID-19 pandemic. This number is consistent with previous cross-sectional paediatric fNIRS studies from our laboratory that have utilised a sample size of between 19 and 25 participants in a group of both NH children (Lawrence et al., 2020; Mushtaq et al., 2019) and paediatric CI recipients (Mushtaq et al., 2020).

3.3.2 Design

3.3.2.1 Order of Testing

A cross-sectional design was employed. For each participant, all study tasks were conducted within one testing session and included:

1) fNIRS scanning whilst performing the Go/NoGo and N-back behavioural EF tasks (approximate duration 15 minutes). Prior to performing the EF tasks, each participant was asked to watch a silent video lasting 5 minutes to acquire resting-state data.
2) A face-to-face assessment of language performance (approximate duration 40 minutes). When originally designing this experiment, an assessment of language performance by an NHS speech and language therapist using the Preschool Language Scale – Fifth Edition (PLS-5^{UK}) was planned for all participants. However, the impact of the COVID-19 pandemic (and its unprecedented demand on NHS clinical services) which commenced six months after the first participant was recruited to this experiment, resulted in the speech and language therapists being unable to perform the

PLS-5^{UK} assessment for participants recruited to this cross-sectional experiment after the onset of COVID-19.

3) Due to the inability to continue with the PLS-5^{UK} assessment, a parent-reported measure of language and communication, The Children's Communication Checklist (CCC-2), was administered to parent/guardians of all participants recruited after the onset of the COVID-19 pandemic (approximate duration 5 to 15 minutes).
4) A Parent-reported measure of EF, the Behaviour Rating Inventory of Executive Function (BRIEF) checklist (approximate duration 10 to 15 minutes).

In total, the tasks within each testing session took between one and one and a half hours for each child participant to complete, including breaks when needed. The parent-reported measures took an additional 15 to 30 minutes to complete.

3.3.2.2 Testing Conditions

All behavioural and simultaneous fNIRS testing was carried out in a double-walled sound-attenuated room (IAC Ltd, Hampshire UK), with fabric-lined walls, a mineral tile ceiling and carpeted floor. A room temperature of 23^{o}C was maintained to provide comfortable testing for the participants. For both the resting-state and behavioural Go/NoGo and N-Back tasks participants were seated in front of a visual display unit (VDU) at a viewing distance of approximately 75cm. The younger participants tended to sit on the

lap of their accompanying parent/guardian, whereas some of the older children preferred to sit alone. All stimuli were presented, and scored where appropriate, using the MATLAB® computing environment (Release 2014b, The MathWorks, Natick, MA). Participants, and where relevant the parent/guardian, were given verbal instructions for all the tasks. Details of neuroimaging and behavioural testing are described below.

3.3.3 fNIRS Testing

Resting-state and behavioural EF task-evoked cortical responses were non-invasively measures using a Hitachi (Tokyo, Japan) ETG-4000 continuous-wave fNIRS system. The ETG-4000 measures simultaneously at wavelengths of 695 nm and 830 nm (sampling rate 10 Hz) and uses frequency modulation to minimise crosstalk between channels and wavelengths (Scholkmann et al., 2014). fNIRS measurements were made with a total of 33 optodes arranged in a 3 x 11 array within an elasticated fabric head cap. The array comprised 17 emitter and 16 detector optodes with a fixed inter-optode distance of 30mm (see Figure 3.1), providing a penetration depth into the brain of approximately 15mm (Gibson et al., 2005; Strangman et al., 2014). This resulted in a total of 52 measurement channels, primarily covering the frontal and temporal cortex bilaterally. A dense sound-absorbing screen was placed between the fNIRS equipment and the participant position, resulting in a steady ambient noise level of 38 dB SPL (A-weighted).

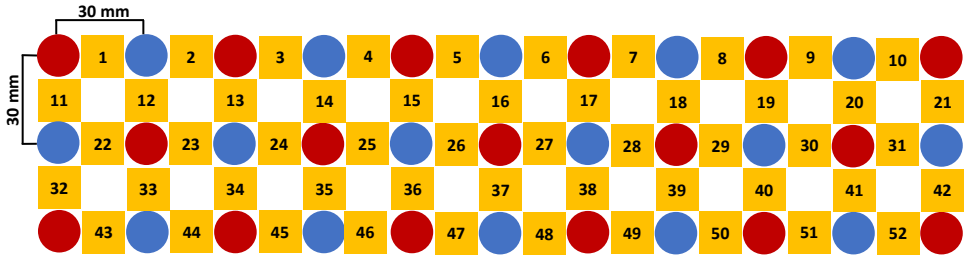


Figure 3.1: A schematic of the 3 x 11 fNIRS optode array. Emitters are depicted in red and detectors in blue. The fixed inter-optode distance of 30 mm is indicated. The 52 measurement channels are represented in yellow and labelled numerically.

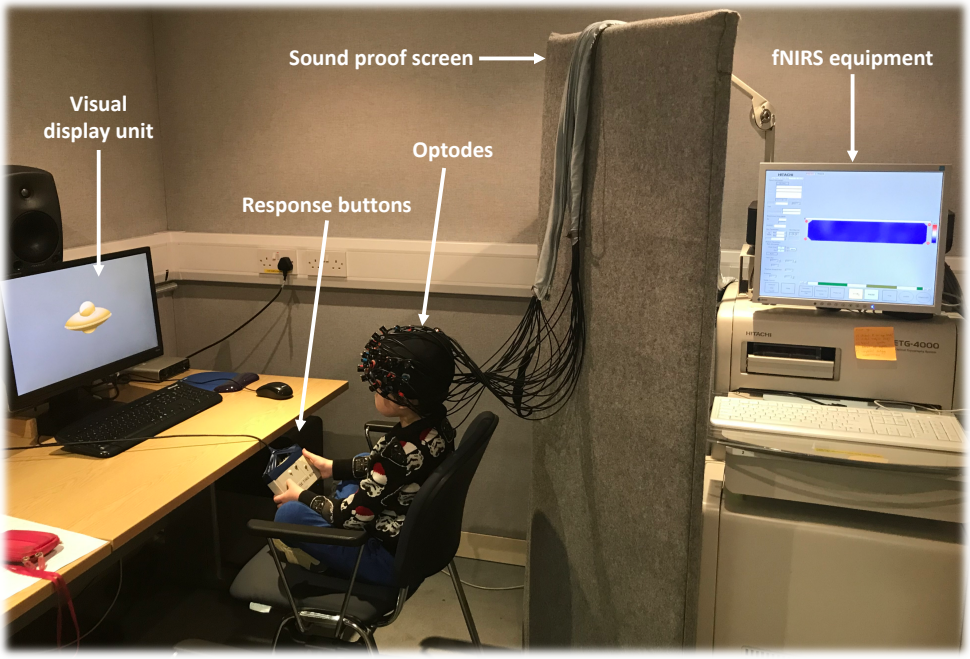


Figure 3.2: The fNIRS experimental set-up in a sound-attenuated room.

The fNIRS experimental set-up is displayed in Figure 3.2 and the specific procedures for acquiring resting-state and behavioural EF-evoked brain activation data are detailed below. Participants were encouraged to sit as still as possible to reduce the occurrence of motion artefacts throughout the duration of all fNIRS measurements. Parent/guardian(s) were instructed to remain as

quiet as possible throughout fNIRS scanning to minimise auditory stimuli, and although it was ideal for participating children to do the same, a modest balance had to be maintained to prevent frustration and non-compliance throughout the tasks. Whilst performing the Go/NoGo and N-Back tasks, participants entered their responses using an "RTbox" button box (Li et al., 2010) as shown in Figure 3.2.

3.3.3.1 Acquisition of Resting-State Data

As previously discussed, resting-state brain activity refers to spontaneous cortical haemodynamic changes during a period of quiet alertness and attention and evidence has shown measures of resting-state connectivity are able to predict later cognitive and language skills in children (Benasich et al., 2008; Broomell et al., 2019; Smith & Bell, 2010). Stimuli used to elicit data during the physiological resting-state aim to achieve the same affective and cognitive state in all study participants (Bell & Cuevas, 2012). A commonly used method of acquiring resting-state neuroimaging data in infants and young children is to show a short video.

Researchers have found this an effective technique due to limited gross motor movements (and hence less associated motion artefact) by paediatric subjects whilst they observe a video clip (Bell & Cuevas, 2012; Whedon et al., 2020). The opening scene of the Disney film *Lion King* was chosen for this 5 minute resting-state experiment because none of the characters speak during the

selected clip. The video was also played in silent on the VDU, hence all auditory and visual (silent speechreading) speech stimuli were removed.

A recent review of paediatric studies that have used fNIRS to acquire resting-state data showed that duration of scanning varied between 1.5 and 60 minutes (Hu et al., 2020). Most of these studies utilised functional connectivity (FC) analysis. A study specifically designed to elicit the minimum resting-state fNIRS imaging duration in children reported that FC was accurately and stably achieved after 7 minutes, yet a minimum duration of 2.5 minutes was sufficient at low network thresholds (Wang et al., 2017). The only published study that has used Phase Transfer Entropy (PTE) to analyse resting-state connectivity involved adult subjects who underwent 5 minutes of fNIRS scanning (Urquhart et al., 2020). A scanning time of 5 minutes was chosen for this resting-state experiment, as according to the available evidence, this would enable suitable analysis of the data using PTE methodology (see Section 3.5.3).

3.3.3.2 Behavioural Stimuli

The Go/NoGo and N-back tasks were employed to examine behavioural EF-evoked fNIRS responses. As outlined in Chapter 2 of this thesis, these tasks have been commonly employed in neuroimaging studies examining IC (Go/NoGo) and visual WM (N-back). Although CF reportedly emerges between 3 and 4 years of

age, children in this age range experience difficulty switching between tasks with more complicated rules (Espy, 1997). The ability to succeed on more complex CF tasks begins to improve when children reach 7 years old (Anderson, 2002). Participants recruited to the cross-sectional experiment in this thesis may therefore have not been capable of performing more complicated versions of a CF task. Although it would have been beneficial to examine behavioural EF-evoked responses to verbal WM, evidence-based measures of such are only validated in children beyond 6 years of age (Wechsler, 2014). Furthermore, evidence from the longitudinal study by Kronenberger et al. (2020) showed that visual WM performance can predict later language outcome. The methodology and stimulation paradigms for the Go/NoGo and N-back tasks that were utilised by the Smith et al. (2017) fNIRS study were implemented in this cross-sectional experiment.

3.3.3.2.1 Behavioural Task: Go/NoGo

In this task, yellow and purple spaceships appeared sequentially on the visual display unit (VDU). Participants were instructed to press a button on the "RTbox" response box when they saw a yellow spaceship, and not when they saw a purple spaceship (see Figure 3.3). A mandatory practice session with both yellow and purple spaceships was completed and repeated, if necessary, until the child attained a score of $\geq$ 70% correct. Subsequently, each participant was presented with four Go blocks (control condition) alternating

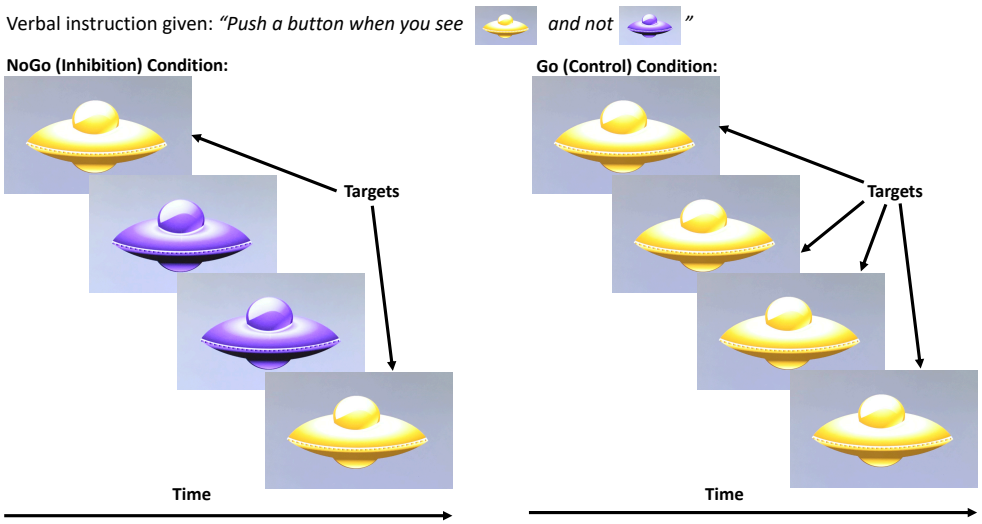


Figure 3.3: The response inhibition control Go/No-Go Task. Figure adapted from Smith et al. (2017).

with four NoGo blocks (inhibition condition) with 10 seconds of rest between each block. The Go blocks included only yellow spaceships, accounting for basic visual processing and motor response. During the rest block a fixation cross was presented on a uniform background. The NoGo blocks included both yellow and purple spaceships at a ratio of 10:4. For all blocks, 10 spaceships appeared for 500 milliseconds (ms) with an inter-stimulus interval of 1000 ms, for a total of 15 seconds per block, with 10 seconds of rest between blocks.

3.3.3.2.2 Behavioural Task: N-back

The N-back task consists of a WM condition (1-back) and a control condition (0-back). For the 1-back condition, various black shapes (square, circle, triangle, star) on a uniform background were presented to participants who were instructed to push a button if they saw the same shape twice in a row (see Figure 3.4). Stimuli

were presented for 1500 ms each with an inter-stimulus interval of 500ms. Practice blocks were completed until a score of $\geq$ 70% correct was obtained. The participant then completed four blocks of 16 seconds each with a target/non-target ratio of 3:5. During the 0-back blocks, participants were told to press a button whenever they saw a circle (an example circle was shown prior to onset of the block). Four 0-back blocks were completed, each block lasting 16 seconds with a target/non-target ratio of 3:5. A 10 second rest period occurred between all blocks.

As per Smith et al. (2017), behavioural analyses for the Go/NoGo and N-back tasks involved calculating average reaction time (RT) and reaction time variability (RTV, the standard deviation of the RT variable for each participant) for correct responses. Trials were excluded if they were associated with a reaction time below 100 ms or above 1000 ms. Overall task accuracy was determined using d'prime, which was calculated using the following formula:

$$\text{d'prime}(p_i) = z(\text{omission error}_i) - z(\text{comission error rate}_i)$$

where z is the z score for the i^{th} participant, omission error rate (OER) represents not pressing the response button when seeing a yellow spaceship and commission error rate (CER) reflects pressing when seeing a purple spaceship. d'prime is known to represent task accuracy while accounting for different response styles (Macmillan & Creelman, 2004).

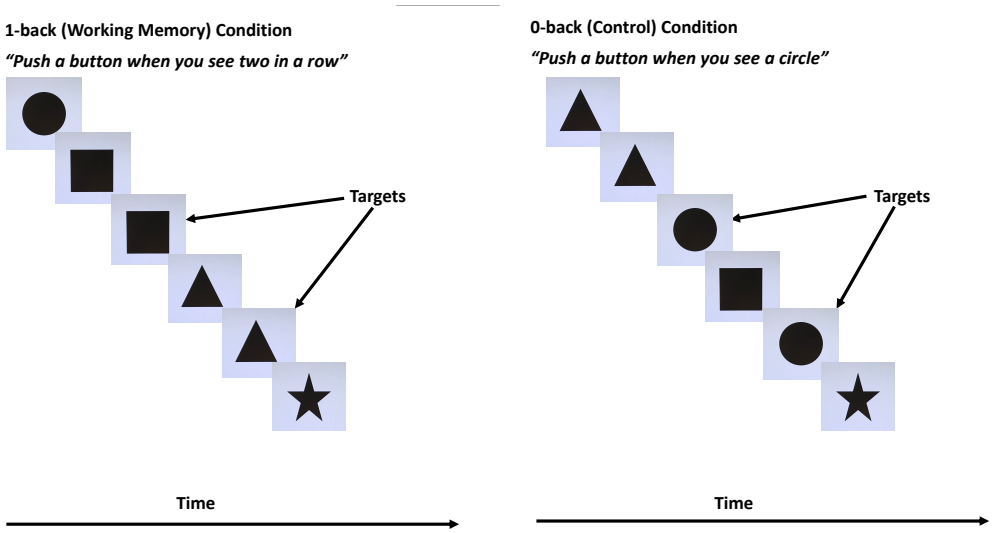


Figure 3.4: The working memory N-back task. Figure adapted from Smith et al. (2017).

3.3.3.3 fNIRS Optode Placement

The fabric heap cap containing the array was positioned on each participant's forehead such that the emitter and detector optodes were centred horizontally at Fpz based on the international 10-20 coordinate system (Jasper, 1958), a rationale commonly used in established fNIRS studies that have specifically examined EF-evoked cortical activation (Perlman et al., 2016; Smith et al., 2017). Specifically, the bottom middle detector was carefully placed at location Fpz and the bottom row of optodes on each side aligned with the trajectory from Fpz and Oz (see Figure 3.5). The optode array ensured good coverage of frontal and temporal cortex bilaterally, where EF and auditory processing are primarily reported to occur (Hickok & Poeppel, 2007; Smith et al., 2017).

Although the array was constantly centred at Fpz, the inter-optode distance was fixed and hence the location of all other optodes was

approximate and depended on the size and shape of each participant's head. To evaluate variation in head size between individuals, the following measurements in centimetres were made on all participants: 1) head circumference, with the measurement taken along the trajectory of Fpz to Oz bilaterally; 2) the nasion to inion distance, and; 3) the distance between pre-auricular points. These measurements showed modest variability amongst participants and allowed for cross-referencing between the international 10-20 system and corresponding Brodmann areas (see section 3.5.4 for further detail). Ideally, optode positions would have been digitised at the time of data collection for each participant. However, due to the unreliable behaviour of the Hiatchi ETG-4000's electromagnetic 3D Probe Positioning Unit within the confines of the sound booth in which testing took place (likely due to the sound-attenuated room's metal doors being in close vicinity of the magnetic receiver and transmitter unit), in addition to the substantial patience and compliance that would have been required from all children, the digitisation procedure was omitted.

Once the arrays had been positioned, the optodes were connected and the Hitachi ETG-4000's 'Auto Gain' function was used to verify that the correct level of light intensity was being output and detected by each source-detector pair.

Figure removed

Figure 3.5: Placement of the fNIRS measurement array. a) Photographic illustration of optode array placement with the emitter optode locations in red and detector optode locations in blue. The bottom centre optode (indicated by yellow

circle) is placed at Fpz, which is located at 10% of the nasion to inion distance away from the nasion (indicated by the yellow dot); **b)** The yellow dashed line indicates the trajectory from Fpz to Oz, which was used to guide placement of the lowermost row of optodes; **c)** and **d)** provide schematics of the international 10-20 positioning system on which the optode array positioning is based.

3.4 LONGITUDINAL fNIRS EXPERIMENT

3.4.1 Participants

A group of severe to profoundly deaf child children and a group of hearing children were recruited to this experiment. Common inclusion criteria across both groups were:

1) Native English speakers
2) Normal or corrected-to-normal vision
3) Aged between 6 months and 3 years and 11 months

Any known cognitive, motor, or language disorder (for example specific language disorder) were defined as exclusion criteria.

3.4.1.1 Normal-Hearing Children

Twenty-eight hearing children were recruited to this study. The group comprised 17 males and 11 females with a mean age of 2.3 years (range 8 months to 3.7 years, SD = 0.97 years) at the time of recruitment. As per the NH participants recruited to the cross-sectional fNIRS study, these longitudinal subjects were recruited with the aim of investigating the relationship between EF and language in typically-developing children, and not for the purpose of performing statistical between group comparisons with CI

participants. Where direct comparisons are made between NH and CI subjects in upcoming chapters, this is on a qualitative and descriptive case study type basis. As described in section 3.3.1.1, all participants had parent-reported normal hearing. The methodology for recruitment of these subjects was the same as described in section 3.3.1.1.

3.4.1.2 Paediatric Cochlear Implant Candidates

Four profoundly deaf paediatric CI candidates were recruited to the study. This group consisted of two male and two female participants with a mean age of 1.9 years (range 8 months to 3.6 years, SD = 1.4 years) at the time of recruitment. The recruiting sites included: 1) the Nottingham Auditory Implant Programme (NAIP), located in the same NHS building as the research site; 2) the Manchester Auditory Implant Programme; 3) the Midlands Auditory Implant Programme, and; 4) St George's Cochlear Implant Programme. At NAIP, a researcher (Dr Rachael Lawrence) attended the relevant outpatient clinics to approach potential participants and their parent/guardian(s). The other auditory implant programmes were ethically approved participant identification centres (PICs), and the parent/guardian(s) of any suitable participants were given a participant information sheet by a member of the clinical team and asked to contact a researcher (Dr Rachael Lawrence) for more information about the study if they so wished.

Additional inclusion criteria for these participants were: 1) deemed a suitable candidate for cochlear implantation by the clinical team at the relevant auditory implant programme; 2) parent/guardian consent to receive bilateral CIs, and; 3) absence of any structural abnormalities which may impact upon CI outcome (as assessed by structural MRI scans taken during clinical assessments).

3.4.1.3 Determining Sample Size

The sample size for this longitudinal study was determined by implementing the same principles utilised for the cross-sectional study, as described in section 3.3.1.3. However, as this longitudinal research was dependent on a high level of cooperation from participants, we also factored in for an attrition rate of 10%. Prior to the impending COVID-19 pandemic, a recruitment target of 20 participants for each of the CI and NH group of children was therefore set. Previous longitudinal fNIRS studies in adult CI recipients from our laboratory involved a sample size of 17 patients (Anderson et al., 2017, 2019). When designing this study, evidence from longitudinal paediatric fNIRS studies was lacking. Hence, our recruitment target was consistent with published literature for adult fNIRS studies of a longitudinal design.

3.4.2 Design

A longitudinal repeated-measures design was employed. The pre-COVID-19 plan for this experiment was to administer various tasks at three time points for the NH subjects and four time points for the

CI candidates. The originally proposed timeline of the research testing sessions for each group are illustrated in Figure 3.6 and Figure 3.7. However, as previously alluded to, testing intervals were severely disrupted by COVID-19. As a result of the pandemic

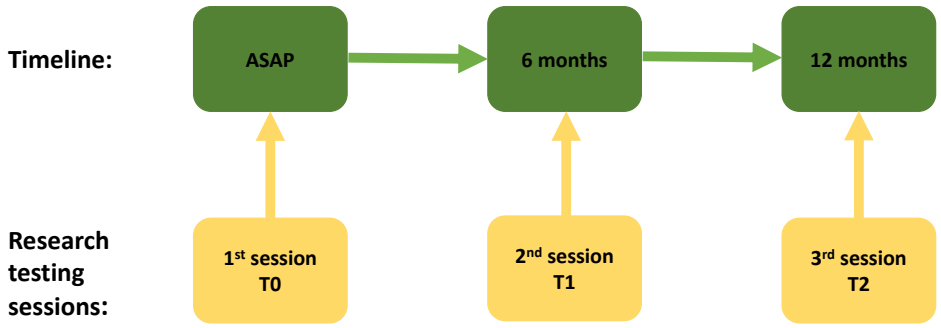


Figure 3.6: Originally proposed timeline of the research testing sessions for longitudinal NH participants.

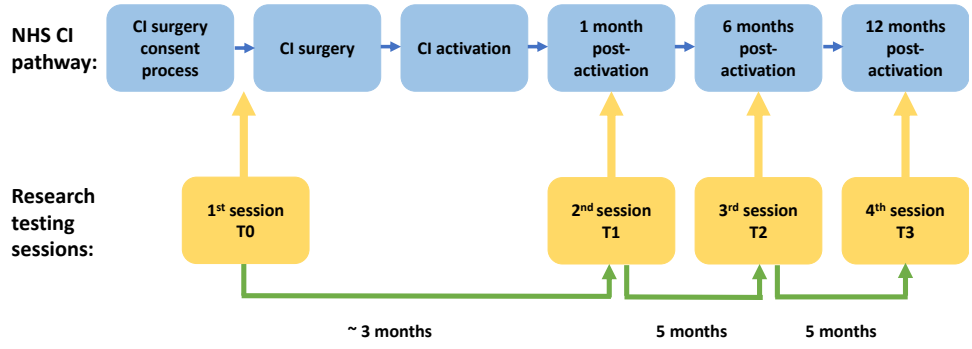


Figure 3.7: Originally proposed timeline of the research testing sessions for longitudinal CI participants in relation to the NHS clinical CI pathway.

induced pause in research activity, most participants attended at two time points only, with face-to-face sessions arranged only when UK government guidance permitted.

3.4.2.1 Testing Intervals

Once consented to receive CIs, the first testing session (T0) for the CI subjects occurred as soon as convenient for the participant and their parent/guardian(s), but prior to implantation surgery. At T0, CI participants were tested in their best-aided condition, i.e. wearing their conventional listening devices. The second (T1), third (T2) and fourth (T3) testing sessions were originally scheduled to occur approximately one, six and twelve months after CI device activation.

As shown in Figure 3.6, it was originally planned for NH subjects to be tested at three time points. Although performing between group comparisons was not a primary aim of this thesis, the retest intervals for the NH participants were planned to be similar to those of the CI group. For example, the final testing sessions were scheduled to take place approximately twelve months and thirteen months after the first testing session for the NH subjects and CI recipients respectively. CI participants were planned to undergo one additional testing session in comparison with NH subjects. The aim of this additional session was to detect any rapid changes in cortical correlates of EF or brain connectivity in response to CI device activation.

3.4.2.2 Order of Testing

At each time point, each participant performed an age-appropriate behavioural EF task whilst wearing fNIRS equipment. As described for the cross-sectional subjects in section 3.3.2.1, this was preceded by a 5 minute period of fNIRS scanning (during which the participants watched the same silent video), enabling the acquisition of resting-state data. With respect to the NH participants, the pre-COVID-19 plan was for each participant to undergo a face-to-face PLS-5^{UK} language assessment with an NHS speech and language therapist at their final 12 month research session (T2). At the time of designing the methodology for this experiment, all recruiting auditory implant programmes were routinely performing a PLS-5^{UK} assessment at 12 months post-activation for all CI recipients, hence the plan was to acquire the result of this language assessment as its timing would have coincided perfectly with the final T3 session for the CI participants.

However, a contingency plan for acquiring language performance data (for the purposes of this thesis) had to be made once the COVID-19 pandemic halted face-to-face research activity and any planned PLS-5^{UK} assessments. An age-appropriate parent-reported measure of language as detailed in section 3.6.3 was therefore implemented. Even when face-to-face research activity was permitted to recommence, as already described, the NHS speech and language therapists no longer had the capacity to perform the PLS-5^{UK} assessments for the purpose of this thesis work alone. As

COVID-19 emerged prior to the final scheduled research session for all longitudinal participants, a parent-reported measure of language was therefore completed by a parent/guardian of every NH and CI subject. Depending on the age of the child, this consisted of either the MacArthur-Bates Communicative Development Inventories (CDIs) - 2nd Edition, (Fenson et al., 2006) or The Children's Communication Checklist (CCC-2) - 2nd Edition (Bishop, 2003). Whilst face-to-face research sessions were suspended, the relevant language measure form was posted out to a parent/guardian of each participant for completion at home. The parent/guardian was asked to fill out the form as close as possible to the originally scheduled final testing session, hence the T2 and T3 sessions for the NH and CI subjects respectively. For those participants who were able to attend their final (T2/T3) face-to-face session at the originally scheduled time, a parent/guardian was asked to complete the parent-reported measure of language at that research appointment.

Parent/guardians were also requested to complete the BRIEF tool as close as possible to the originally scheduled final (T2/T3) research session. The form was either sent out via post along with the language parent-reported measure form or was completed during the final face-to-face research session if the COVID-19 pandemic allowed for this to occur at the appropriately scheduled time.

3.4.2.3 Testing Conditions

The testing conditions for these participants were the same as those described in section 3.3.2.2.

3.4.3 fNIRS Testing

3.4.3.1 Acquisition of Resting-State Data

Resting-state data was acquired according to the protocol described in section 3.3.3.1.

3.4.3.2 Behavioural Stimuli

The following behavioural EF tasks were employed during fNIRS scanning. If a participant was non-compliant with the fNIRS head-cap, then behavioural performance data alone were acquired where the subject allowed.

3.4.3.2.1 Behavioural Task for Age Range 6 – 23 Months: A-not-B Task

The A-not-B task evaluates the WM and IC elements of EF. Participants in this age group were tested according to an adapted version of an A-not-B testing paradigm devised by (Cuevas & Bell, 2010). The A-not-B task was chosen not only because it is commonly used for obtaining behavioural measures of EF, but also for examining neural mechanisms of EF development in children aged 6 to 24 months (Cuevas & Bell, 2010, 2014; Morasch & Bell, 2011).

In terms of the equipment set-up for this task, a testing table was brought into the sound-booth and placed between the researcher and the participant who was sitting on the lap of the accompanying parent/guardian (see Figure 3.8). The participant was firstly tested on object permanence by asking them to find an attractive toy on the table that was partially covered with one cloth, then completely covered with one cloth, then hidden under one of two identical cloths (Uzgiris and Hunt, 1975). The onset of a trial was deemed to be the point at which the cloth(s) were placed on the toy/table, which was marked by the researcher pressing the "RTbox" response box.



Figure 3.8: The fNIRS experimental set up for the A-not-B task. The photographs in this illustration were taken for demonstrative purposes only, hence the fNIRS head-cap isn't being worn in these images. However, the fNIRS head-cap can be seen in easy reach of the participant. As seen in image **a)** an attractive toy (red ball) was placed in a well at location A that was subsequently covered with a cloth as shown in image **b)**. The parent/guardian was instructed to prevent their child from reaching to find the toy until instructed to so by the researcher. If a child successfully found the toy at location A [as seen in images **c)** and **d)**] on two successive trials, the toy was then hidden at the well in location B [as shown in **e)**]. If a participant successfully recovers the toy from location B [as shown in image **f)**] on two out of three A–A–B trials, they were then deemed competent at that level of the performance scale and were subsequently tested with an increasing time delay.

If a participant achieved successful performance with object permanence, then he/she was subsequently challenged with the A-not-B task. During the A-not-B task, on the testing table were two hiding wells, named location A and location B (see Figure 3.8). In view of the participant, an attractive toy was firstly hidden in location A. Once the toy was hidden, a cloth was placed over each well and once covered the participant was then immediately allowed to search for the toy without a time delay. Like object permanence testing, the onset of a trial commenced when a cloth was placed over both wells and was marked by a researcher pressing the "RTbox" response box. After two successful retrievals at side A, the toy was then hidden in location B. Participants who successfully recovered the toy from location B on two out of three A–A–B trials, and hence did not make the A-not-B error, were then tested with a 2 second delay (the delay being the time between covering the wells and the participant being allowed to reach for the hidden toy). Subsequent delays up 10 seconds were initiated until the participant made the A-not-B error on two out of three trials at any given delay. Delay was incremented in 2 second intervals throughout the study. For delays of 2 seconds or longer, the researcher called to the participant to break their visual fixation on the correct well, and the parent/guardian held the participant's arms and torso firmly to prevent them moving or straining toward the correct well. The participant was allowed to reach and find the toy after the specific time delay elapsed, which was marked by a cue from the researcher who said aloud *"Where's the toy?"* at which point the

parent/guardian also released the participant's hands. To be declared competent at any given delay, a participant was required to successfully retrieve the toy from location B in two out of three A–A–B trials.

Electronic correspondence from Professor Martha Ann Bell, Professor of Psychology, Virginia Tech, USA advised that going beyond a 10 second delay risks testing long-term memory function. Hence, in her world-renowned laboratory this is the maximum delay used with the A-not-B task. To extend A-not-B testing up to 23 months of age, on the advice of Professor Bell, the A-not-B with invisible displacement was performed for any participant who reached competence for the A-not-B task with 10 second delay. Invisible displacement involved the participant watching an attractive toy being hidden in a central location under an opaque cup. The cup, and hence the hidden toy, was moved to one side of the testing table, location A (which marked the onset of the trial). The participant was given sufficient time to visualise where the cup finally ended up being located on the table. An opaque barrier was then placed in front of the cup and a 5 second delay imposed. During the delay and behind the barrier, a second identical cup was placed on the table, location B. The barrier was then removed and the infant allowed to search for the toy under the cup. Once the infant achieved two correct same-side findings, the hiding location was reversed (A-A-B) to provide an inhibitory challenge. As per the standard A-not-B task, to be declared competent, the participant

was required to successfully reach to B location in two out of three A–A–B trials.

Evaluation of participants' performance on each individual A and B trial allowed analysis of the proportion of correct responses (% correct) on non-reversal (A) and reversal (B) trials (Cuevas & Bell, 2010). As shown in Table 3.1, an evidence-based scale of A-not-B task performance, including object permanence, was also constructed to facilitate analysis of the data acquired for this task (Cuevas & Bell, 2010; Diamond, 1985; Kermoian & Campos, 1988; Uzgiris & Hunt, 1975). Data were subjected to statistical testing, where appropriate, as outlined throughout the thesis.

3.4.3.2.2 Behavioural Task for Age Range 24 – 47 Months: Tongue Task & Mommy/Me Task

Although tasks that examine the CF element of EF, such as the DCCS task (Zelazo, 2006), are suitable for children aged 36 months and older, we continued to utilise tasks that assessed IC and WM in children aged up to 47 months. This enabled the same core elements of EF to be consistently evaluated in this longitudinal experiment, and more importantly, throughout the thesis. Furthermore, IC and WM have previously been reported as the elements of EF that best represent the function of the PFC (Roberts & Pennington, 1996).

Table 3.1: The performance level scale for the A-not-B task

Performance Level	Definition
1	Fails to locate an object partially covered with one cloth
2	Successfully locates object partially covered with one cloth
3	Successfully locates object completely covered with one cloth
4	Successfully locates object hidden under one of two identical cloths
5	Competence for A-not-B task with 0 second delay
6	Competence for A-not-B task with 2 second delay
7	Competence for A-not-B task with 4 second delay
8	Competence for A-not-B task with 6 second delay
9	Competence for A-not-B task with 8 second delay
10	Competence for A-not-B task with 10 second delay
11	Competence for A-not-B task with invisible displacement

Taken and adapted from Cuevas & Bell (2010); Diamond (1985); Kermoian & Campos (1988); Uzgiris & Hunt (1975).

Adapted versions of the tongue task (Cuevas, Hubble, et al., 2012; Kochanska et al., 2000) and mommy/me task (Bell & Wolfe, 2007) were utilised not only because they are quick and easy to administer (making it easier for the researcher and less tiresome for the participant), but also because behavioural performance on both these tasks have been shown to significantly correlate with neural mechanisms of EF in longitudinal (EEG) studies (Broomell et al., 2019). Task performance for both the tongue and mommy/me task was analysed via the proportion of correct trials (% correct). Where appropriate, data were subjected to statistical testing as outlined throughout the thesis.

3.4.3.2.2.1 The Tongue Task

During the adapted version of the tongue task, the participant was asked to hold an edible item for 10, 20 and finally 30 seconds before being allowed to eat it. The methodology for this task formally involves a participant holding the edible item on their tongue (Cuevas, Hubble, et al., 2012; Kochanska et al., 2000), however to maximise safety and prevent aspiration of the item into the airway (albeit unlikely) the participant was instead instructed to hold the item in their hand until verbally instructed to eat it. The participant underwent three trials at each time delay, hence a total of nine trials for the task. The onset of a trial was determined by the participant taking the sweet in their hand and marked by the researcher pressing the "RTbox" response box. A successful trial was determined by the participant not eating the item within the specific time delay.

3.4.3.2.2.2The Mommy/Me Task

This task required a participant to remember two rules and exhibit IC by performing a subdominant response. At the beginning of the session, individual photographs of the child participant and the parent/guardian were taken. The child was instructed to say "mummy", "daddy" or their guardian's name when shown a photograph of themselves and to say "me" when shown a photograph of their parent/guardian. The participant was firstly given two learning trials (one containing the parent/guardian photograph the other using the child photograph) after which

feedback was given for any incorrect response. Secondly, ten test trials (five with the parent/guardian photograph and five with the child photograph arranged in a pseudorandom order) were administered in which no feedback was given.

3.4.3.2.3 Behavioural Task for ≥ 48 Months: Go/NoGo & N-back Task

As all participants were aged under the age of 48 months at the time of recruitment, this test was not performed at the T0 session for any participant. However, if a child was aged 48 months or older at any of the subsequent testing sessions (T1/T2/T3), the Go/NoGo and N-back tasks were administered as described in section 3.3.3.2.

3.4.3.3 fNIRS Optode Placement

The fNIRS optode array placement in this longitudinal experiment followed the same principles as described in section 3.3.3.3.

3.5 ANALYSIS OF fNIRS DATA

Analysis of fNIRS data was performed in MATLAB (MathWorks, Natwick, MA) using functions in the HOMER2 package (Huppert et al., 2009) together with custom scripts. The analysis was performed in a similar manner to previous studies conducted in our laboratory (Anderson et al., 2017; Lawrence et al., 2018; Lawrence et al., 2020; Mushtaq et al., 2019; Wiggins et al., 2016; Wiggins & Hartley, 2015; Wijayasiri et al., 2017). The following steps were performed.

3.5.1 Pre-Processing Steps

First, channels with poor signal quality were excluded. The scalp coupling index (SCI) was used to identify and exclude channels suffering from poor optode-scalp contact (Pollonini et al., 2014). We excluded channels with SCI <0.3, chosen to exclude only the worst 5% of channels in our dataset. Experience from previous studies in our laboratory showed that excluding only the worst 5% of channels strikes an appropriate balance between the desire to include only high-quality channels in the analysis versus the risk of committing type II (false negative) statistical errors if the effective sample size is too heavily reduced due to extensive channel exclusions.

Next, the measured light intensity levels were converted to optical density using HOMER2 *hmrIntensity2OD* function, a standard step in fNIRS data analysis (Huppert et al., 2009). Once the raw fNIRS intensity signals had been converted, wavelet filtering was conducted using the HOMER2 *hmrMotionCorrectWavelet* function to allow for motion-artefact correction (Molavi & Dumont, 2012). In this approach, the influence of motion artefacts is reduced by eliminating outlying wavelength coefficients, which are assumed to represent artefacts. Wavelet coefficients lying more than 0.719 times the interquartile range below the first or above the third quartiles were excluded. By avoiding the need to reject contaminated trials from the data, and instead processing the signals to directly suppress artefacts, wavelet filtering can enhance

data yield (Molavi & Dumont, 2012). An example of the effect on wavelet filtering on the fNIRS signal is provided in Figure 3.9.

Following motion-artefact correction, optical density signals were band-pass filtered between 0.02 and 0.5 Hz to attenuate cardiac oscillations and low-frequency drift. Optical density signals were then converted into estimated changes of HbO and HbR through the application of the modified Beer-Lambert law (Huppert et al., 2009). A default value of 6 was used for the differential path-length factor at both wavelengths. The continuous-wave fNIRS system used in both the cross-sectional and longitudinal experiments allowed for the estimation only of relative changes in haemoglobin concentrations across conditions and not absolute concentrations.

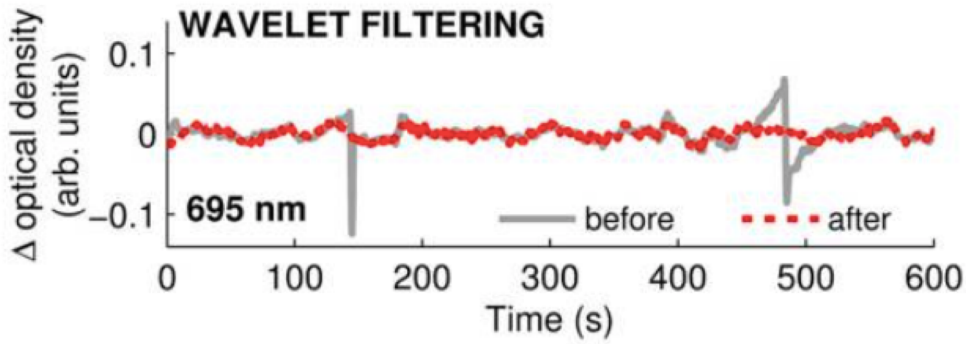


Figure 3.9: A representative example of the wavelet filtering pre-processing stage. Motion artefacts typically manifest as abrupt spikes in the fNIRS signal due to movement and subsequent decoupling between the optodes and the scalp. Spikes from the optical signal are successfully removed, whilst parts of the signal that are not contaminated by motion artefact remain unchanged. Taken from Wiggins & Hartley (2015).

The haemodynamic modality separation (HMS) algorithm described by (Yamada et al., 2012) was applied to isolate the functional component of the haemodynamic signal and suppress systemic physiological interference. This algorithm attempts to separate functional and systemic signals based on the assumption that the correlation between HbO and HbR will be different in each case. Specifically, a positive correlation between changes in HbO and HbR is assumed in the systemic component, whereas a negative correlation is assumed in the functional component. Figure 3.10 illustrates the application of this algorithm to fNIRS data (Wiggins & Hartley, 2015). The estimated functional component of the fNIRS signal was extracted and subjected to subsequent processing. Although this approach does not accurately account for all statistical properties of the noise typically found in fNIRS data (Huppert et al., 2009), previous studies from our laboratory have found application of this algorithm to be beneficial to the detection of auditory cortical activation (Lawrence et al., 2018; Lawrence et al., 2020; Wiggins et al., 2016; Wijayasiri et al., 2017). Furthermore, application of the HMS algorithm was shown to substantially improve the test-retest reliability of auditory fNIRS measurements (Wiggins et al., 2016).

3.5.2 Quantifying Amplitude of Cortical Activation

To quantify the level of cortical EF task-evoked response, the pre-processed fNIRS signal was subjected to a general linear model (GLM). The GLM was applied to the continuous data collection over the duration of the imaging session. The design matrix included a

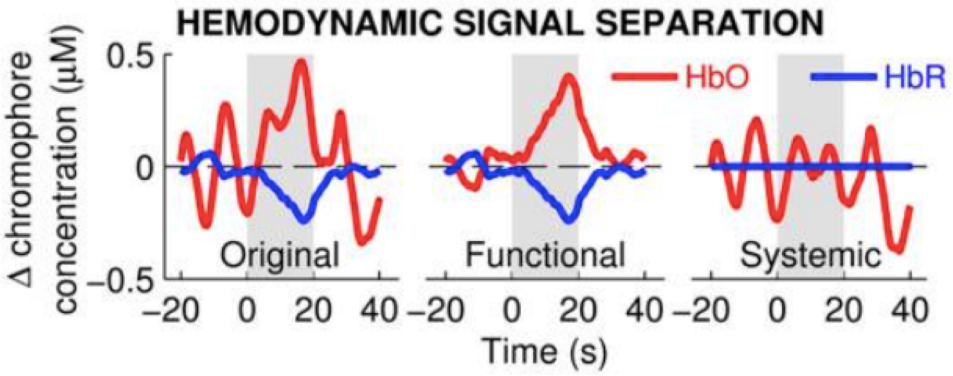


Figure 3.10: A representative example of the haemodynamic modality separation (HMS) algorithm applied to the fNIRS signal. The original haemodynamic response function is contaminated by physiological noise. The HMS algorithm is applied and a functional component becomes apparent, in addition to an estimate of systemic noise interference. Taken from Wiggins & Hartley (2015).

set of three regressors (corresponding to the canonical haemodynamic response plus its first two temporal derivatives) for each experimental condition within each behavioural task, plus a further set for the rest trials within each task where appropriate. The purpose of including the temporal derivative terms is to allow flexibility in the model to capture small differences in the delay and/or duration of the observed haemodynamic response (as compared to the canonical response). Each trial in each behavioural task was modelled as a short epoch corresponding to the actual duration of stimulation for that trial.

The beta weights of the canonical haemodynamic response function (HRF) were extracted at each measurement channel, for each stimulation condition within each behavioural task, and for all participants. The employed haemodynamic signal separation

method (Yamada et al., 2012) assumes a fixed linear relationship between HbO and HbR in the functional response. Therefore, the results of all statistical analyses are identical regardless of whether conducted on the beta weights extracted for the HbO or HbR parameter. In the subsequent results chapters, only results corresponding to the beta estimates of the HbO parameter of the functional component are presented. These beta weights were used to quantify the amplitude of behavioural EF task-evoked cortical activation and were subjected to further statistical analyses that are specified in the upcoming results chapters.

3.5.3 Phase Transfer Entropy Directed Connectivity

Phase Transfer Entropy (PTE) directed connectivity analysis was employed to examine both resting-state cortical connectivity and connectivity on EF task-evoked brain activation between prefrontal and superior temporal regions. Directed connectivity (DC) rather than functional connectivity (FC) analysis was chosen since estimating the effect that one brain region has over another has the potential to provide important information about the specific roles of top-down and bottom-up connectivity in EF and auditory processing. Phase Transfer Entropy was the technique chosen for directed connectivity analysis due its reported robustness to signal noise (Lobier et al., 2014). Furthermore, other methods of DC analysis such as DCM require strong assumptions on underlying connectivity between EF and auditory regions, which as discovered in Chapter 2 of this thesis, are currently not available. The estimation of PTE is

based on the same principle as Granger Causality and involves calculating the difference between the uncertainty of the target signal *Y* conditioned by its past and the uncertainty of the target signal conditioned on both its past and source signal *X* (Cao et al., 2018; Hillebrand et al., 2016; Urquhart et al., 2020). After the necessary pre-processing steps described in section 3.5.1, the specific methodology used by Lobier et al. (2014) was employed to calculate PTE values that reflected estimates of directed connectivity between relevant regions of interest (ROIs). Further details on PTE connectivity analysis are described in the relevant sections of Chapter 6.

3.5.4 Defining Cortical Regions of Interest

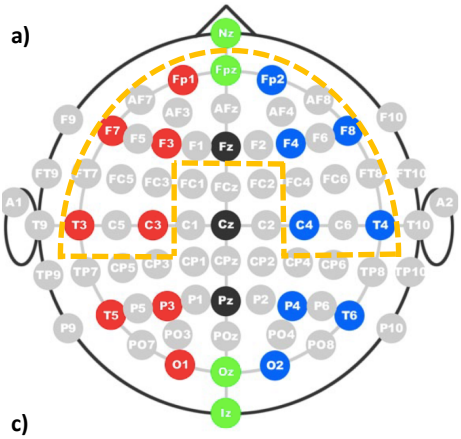
Beta weights corresponding to the channels forming the ROIs were extracted for all conditions in each behavioural EF task, and additionally for the resting-state. These were channels targeting both EF and auditory brain regions in left and right cerebral hemispheres. Defining ROIs for EF was not a straightforward task. As described in Section 2.5, the definition of the anatomical subdivisions of the LPFC varies amongst neuroimaging studies. In the fNIRS study by Smith et al. (2017), to measure cortical responses to behavioural IC and WM tasks, the international 10-20 coordinate system was used to target Brodmann area (BA) 10 and 46 (both located within the LPFC). The international 10-20 system allows correlation of defined external anatomical landmarks with underlying cortical areas (Jasper, 1958). Despite being primarily

designed for EEG to allow electrode placement to be standardised, this system has been widely implemented in fNIRS imaging to guide optode positioning relative to BAs that are referenced as either 10% or 20% of the total front to back, or right to left, distance of the skull. Although Smith et al. (2017) reported BAs 10 and 46 to correspond to the VLPFC and DLPFC respectively, as illustrated in Figure 2.6, other researchers consider BA 10 to be part of the lateral orbitofrontal and lateral frontopolar cortex. Regardless of the controversy surrounding terminology for subdivisions of the LPFC, increased activation overlying BA 10 and 46 (when located via the 10-20 system) has been observed in multiple fNIRS studies examining responses to WM and IC tasks (Perlman et al., 2016; Smith et al., 2017). Therefore, these BAs were targeted for the EF ROIs in both the current cross-sectional and longitudinal experiments. With respect to auditory ROIs, although the primary auditory cortex is located medially within the lateral sulcus (Penhune et al., 1996), secondary auditory regions important for speech processing are located more laterally within the superior temporal cortex (Friederici, 2011). These secondary auditory areas, which include BA 22 and 42, were targeted as auditory ROIs bilaterally across all fNIRS experiments.

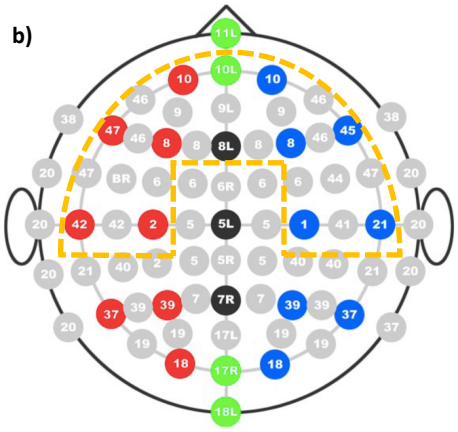
The definition of both EF and auditory ROIs was enabled by the international 10-20 system combined with measurements of participants' head size. As the inter-optode distance within the array remained fixed at 3cm, extrapolated measurements of the distance

of each optode from defined landmarks of the 10-20 system made it possible to determine over which Brodmann area (BA) each fNIRS recording channel was approximately located in participants at the group level. Figures 3.11 and 3.12 show the typical coverage of the 3 x 11 fNIRS optode array for participants in the cross-sectional and longitudinal experiments respectively. These figures also detail the mean distance within each experimental group for: 1) Fpz to Oz; 2) nasion to inion, and; 3) left to right pre-auricular point.

a)



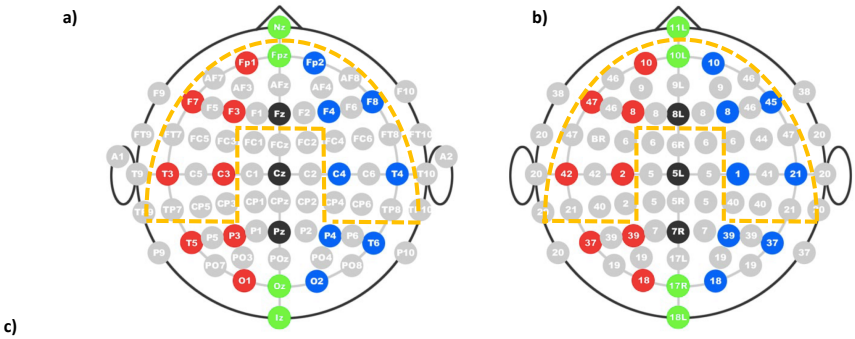
b)



c)

	Fpz to Oz	Nasion to Inion	Left to Right Pre-Auricular Point
Mean Distance (n = 20)	26.0 cm	32.3 cm	32.0 cm
Standard Deviation	1.1 cm	1.8 cm	1.3 cm

Figure 3.11: Typical coverage by the 3 x 11 optode array for all cross-sectional participants with respect to the international 10-20 system and the corresponding Brodmann areas. The area of the brain typically covered by the optode array is indicated by the dashed yellow line in relation to the positions of the International 10-20 system in schematic **a)** and the corresponding Brodmann areas in schematic **b)**. The optode array typically spanned all cortical areas within the yellow dashed line, hence good coverage of the prefrontal and temporal areas was achieved. The mean distance of specific measurements for 20 participants (NH n =18; CI n = 2) along with the standard deviations are shown in table **c)**. The mean distances in this table, in combination with the landmarking system of the international 10-20 system, were used to devise the dashed yellow line in both schematics **a)** and **b)**.



c)

Research Session	Mean age of participants	Mean Fpz to Oz distance	Mean Nasion to Inion distance	Mean Left to Right Pre-auricular point distance
1	26.8 months *SD = 11.8*	24.2 cm *SD = 1.1*	29.8 cm *SD = 3.3*	29.1 cm *SD = 3.0*
2	40.4 months *SD = 12.0*	24.7 cm *SD = 1.1*	30.1 cm *SD = 2.9*	29.8 cm *SD = 2.8*

Figure 3.12: Typical coverage by the 3 x 11 optode array for all longitudinal participants with respect to the international 10-20 system and the corresponding Brodmann areas. The area of the brain typically covered by the optode array across the two research sessions is indicated by the dashed yellow line in relation to the positions of the International 10-20 system in schematic **a)** and the corresponding Brodmann areas in schematic **b)**. The optode array typically spanned all cortical areas within the yellow dashed line, hence good coverage of the prefrontal and temporal areas was achieved. The mean distance of specific measurements for 25 participants (NH n = 22; CI n = 3) along with the standard deviations are shown in table **c)**. The mean distances in this table, in combination with the landmarking system of the international 10-20 system, were used to devise the dashed yellow line in both schematics **a)** and **b)**. Although 28 NH and 4 CI participants were originally recruited to the longitudinal experiment, as detailed in Chapter 4, not all subjects complied with fNIRS testing. The above head measurement data only relates to those participants that underwent fNIRS testing.

Interestingly, the standard deviation (SD) for all these measurements rarely exceeded the fixed inter-optode distance of 3cm. Therefore, at the group level, in both the cross-sectional and longitudinal studies it was calculated that channels #26, 36 and 47 approximately overlaid right BA 10, channels #27, 38 and 48 overlaid left BA 10, channels #25, 35 and 46 overlaid right BA 46 and channels #28, 39 and 49 overlaid left BA 46. The superior temporal cortex (STC) was targeted by channels #32, 33 and 43 in the right hemisphere, and channels #41, 42 and 52 in the left hemisphere. Although parietal areas have been implicated in EF

processing, head measurements indicated that the optode array provided insufficient coverage of this region across all participants in both fNIRS experiments. Nonetheless, the main aim of this thesis was to measure EF-task evoked cortical activation and correlates of brain connectivity in and between prefrontal and temporal regions.

To summarise, the EF ROIs within the LPFC were defined as follows: 1) right BA 10 (channels #26, 36 and 47); 2) left BA 10 (channels #27, 38 and 48); 3) right BA 46 (channels #25, 35 and 46), and; 4) left BA 46 (channels #28, 39 and 49). The right and left auditory ROIs overlying the STC were defined as: 1) right auditory (channels #32, 33 and 43), and; (2) left auditory (channels #41, 42 and 52). A limited number of channels within each ROI was beneficial because previous studies have indicated that fNIRS measurements are more reliable when averaged over a small number of channels that overlie a region of interest (Plichta et al., 2006; Schecklmann et al., 2008). Although the EF and auditory ROIs were defined with the aim of achieving optimal coverage of a desired cortical area, due to the limited spatial resolution of fNIRS and the 3cm emitter-detector distance, it is accepted that these ROIs were also sensitive to haemodynamic changes in neighbouring cortical regions. Therefore, any reference to LPFC or STC activation throughout this thesis reflects the intended ROI coverage (unless otherwise stated) as no definitive conclusions can be drawn about the exact anatomical origin of any observed cortical activation.

3.6 ASSESSMENT OF LANGUAGE AND EXECUTIVE FUNCTION PERFORMANCE

3.6.1 The Preschool Language Scales – 5th edition, UK (PLS-5UK)

The Preschool Language Scales – Fifth edition - UK (PLS-5UK) is an individually administered test that measures children's receptive and expressive language skills (Zimmerman et al., 2014). It was primarily developed for use in children from birth to 7 years and 11 months of age, however it can also be administered to children who are older yet function developmentally within this age range. The PLS-5UK manual states that examiners should be either a speech and language therapist or psychologist, both of whom are deemed to possess the required qualifications to administer, score and interpret the results.

The PLS-5UK assessment consists of two standardised scales and three supplementary, yet optional, measures. The two standardised scales are Auditory Comprehension (AC) and Expressive Communication (EC). The AC scale consists of 65 numbered tasks and evaluates understanding of language, whereas the EC scale is formed of 67 tasks and determines how well a child communicates with others. A total language score (TLS), a combination of the AC and EC score, may also be calculated.

PLS-5UK provides norm-referenced information due to being standardised on a UK population. It is therefore able to evaluate

how a particular child is functioning in comparison to NH peers with both substantial reliability and validity (Zimmerman et al., 2014). The norm-referenced information includes standard scores, percentile ranks, and age equivalents for AC, EC and total language scales at three month intervals from birth to children aged 11 months, and at six month intervals for ages 1 year to 7 years and 11 months. In terms of the standard score, a score of 100 represents the mean performance of a child for a given age interval, with a standard deviation (SD) of 15. Hence, standard scores between 85 and 115 correspond to one SD below and above the mean respectively. Percentile ranks indicate a child's performance in relation to others of the same age in the normative group and range from 0.1 to 99.9. The mean standard score of 100 is at the 50th percentile rank for all ages. Age equivalents indicate the age at which a given raw score is the point at which 50% of the children at a given age achieve higher scores and 50% achieve lower scores. Norm-referenced standard scores are commonly used for identifying language disorders (McCauley and Swisher, 1984) because percentile ranks cluster near the 50th percentile and age equivalents have a number of psychometric limitations (Zimmerman et al., 2014). When norm-referenced standard scores for are used for the purpose of evaluating language performance in the PLS-5^{UK} specifically, the criteria for identifying a disorder may vary across not only amongst examiners, but also clinical centres. As detailed below, the PLS-5^{UK} result for every participant recruited to this thesis was interpreted by an NHS speech and language therapist.

For the purposes of statistical analysis of the data acquired within this thesis, the norm-referenced standard scores for the AC, EC and total language scales were utilised where appropriate.

The original methodology for this thesis was designed prior to the COVID-19 pandemic. The initial plan was to use PLS-5^{UK} for the purposes of assessing language skills in all recruited participants (NH and CI, cross-sectional and longitudinal) for the following reasons: 1) in terms of age, this assessment could be used in all participants, and; 2) it is a clinical assessment tool used by many UK auditory implant programmes (National Deaf Children's Society, 2021). Before the onset of COVID-19, speech and language therapists at all the recruiting auditory implant programmes were performing a PLS-5^{UK} assessment at 12 months after CI activation for all children as part of their routine NHS CI clinical care pathway. The original plan was to use the result of this NHS PLS-5^{UK} assessment for the purpose of the longitudinal experiment within this thesis. The final research session (T3) for longitudinal CI participants was also planned for 12 months after CI activation, hence would have coincided perfectly with the scheduled NHS PLS-5^{UK} assessment.

The PLS-5^{UK} assessment is also used by auditory implant programmes for ongoing annual monitoring of language development in CI recipients for many years after device insertion, again as part of their routine NHS care pathway. To avoid a learning

effect and hence misleading performance results, the PLS-5^{UK} should not be frequently or unnecessarily repeated. It was therefore decided that the fNIRS testing session for the cross-sectional CI participants would be arranged within one month of any scheduled NHS PLS-5^{UK} assessment. If a cross-sectional CI participant was no longer undergoing annual language performance review, then the speech and language therapists at the relevant auditory implant programme had prospectively agreed to perform a PLS-5^{UK} for the purpose of the thesis. This would have ensured that any unexpected language performance in a CI participant was appropriately managed by their own speech and language therapy team. Once again, the plan was to ensure that the fNIRS testing session and the PLS-5^{UK} assessment would occur within one month of each other.

For the longitudinal NH participants, the pre-COVID-19 plan was for these children to undergo a PLS-5^{UK} assessment with a NAIP speech and language therapist at their final research session (T2) scheduled for 12 months after recruitment to the study. In terms of the cross-sectional NH participants, these children were scheduled to have a PLS-5^{UK} with a NAIP speech and language therapist within one month of their fNIRS testing session. Individual NH participant performance on PLS-5^{UK} would be interpreted by the NAIP speech and language therapist performing the assessment. In the event of a concerning PLS-5^{UK} score, prospectively gained ethical approval would enable parental/guardian consent to be sought to for a member of the research team to contact the General Practitioner

(GP) of the relevant participant and advise a referral to a speech and language therapist.

3.6.2 The Impact of COVID-19 on Acquiring Measures of Language Performance

In March 2020, all non-COVID-19 related face-to-face research sessions were suspended due to the COVID-19 pandemic. Faced with an unprecedented pause in face-to-face research activity for an undetermined length of time, an alternative assessment of language performance had to be considered even though 14 already recruited cross-sectional participants had undergone a PLS-5^{UK} assessment. Furthermore, it was anticipated by NAIP speech and language therapists that even when face-to-face research activity resumed, the pressures on the NHS and NAIP would preclude their availability to perform PLS-5^{UK} assessments for the purposes of this thesis alone.

Unfortunately, a non-face-to-face evidence-based tool that encompassed the entire age range of children recruited to this thesis (6 months to 6 years of age) was not available. After seeking advice and guidance from NAIP speech and language therapists, it was decided that either the MacArthur-Bates Communicative Development Inventories (CDIs) - 2nd Edition, (Fenson et al., 2006) or The Children's Communication Checklist (CCC-2) - 2nd Edition (Bishop, 2003) would be utilised to assess language performance in

all CI and NH participants. Both these assessments utilise parent-reported measures of language ability.

3.6.3 Parent-Reported Measures of Language Performance

Although not originally chosen to examine language skills for the purposes of this thesis, parent-reported measures do have advantages over other available assessments. These advantages include: 1) the potential for more robust data on language performance due to parents observing their children in a more diverse set of circumstances and social situations (compared with a standalone clinical assessment by a speech and language therapist); 2) the avoidance of an assessment in the clinical setting being influenced by personality traits such as shyness and transient mood, and; 3) a cost-effective and rapid way of evaluating language ability (Fenson et al., 2006). However, limitations of these measures include possible observer bias and, specific to this research thesis, the fact that the same parent-reported measure couldn't be utilised in all participants due to the wide age range of recruited children. For the longitudinal study, statistical analysis of language data was therefore substantially restricted. Furthermore, at the time of performing the experiments within this thesis, neither an evidence-based nor clinically-validated parent-reported measure for the age range 38 to 47 months was available for use. Despite these limitations, the parent-reported measures of language employed in this thesis were: 1) one of the three MacArthur-Bates Communicative Development Inventories (CDIs) for participants

aged 8 to 37 months, and; 2) the CCC-2 for those aged 48 months and older.

3.6.3.1 The MacArthur-Bates Communicative Development Inventories (CDIs) – Second Edition

The MacArthur-Bates CDIs are widely used parent-reported measures that enable assessment of early language development (Fenson et al., 2006). There are three versions of the CDI, all of which are in American English, and each target a defined age range. A parent or guardian is asked to fill in the relevant CDI form and given instruction to indicate which words and/or sentences in a prespecified list their child can already understand and/or produce. The three versions of the CDI are: 1) the CDI-Words and Gestures (CDI-WG), which is used to assess vocabulary comprehension and production in addition to communicative gestures in children aged 8 to 18 months; 2) the CDI-Words and Sentences (CDI-WS) that enables assessment of productive vocabulary and early use of grammar, including sentence complexity and the mean length of the longest utterances in children aged 16 to 30 months, and; 3) the CDI-III, a short and brief measure used to assess language development in children between 30 and 37 months, which consists of an assessment of productive vocabulary, expressive sentence complexity and language use including questions about semantics and syntax.

To discuss these three versions in more detail, in terms of the CDI-WG this form consists of two major parts: 1) Part I: Early Words, a

396 item vocabulary checklist in which parents indicate words their child understands and says, and; 2) Part II: Actions and Gestures, focusing on use of communicative and symbolic actions and gestures, hence skills independent of verbal expression. The CDI-WS also has two parts: 1) Part 1: Words Children Use, containing a 680 word vocabulary checklist, and; 2) Part II: Sentences and Grammar that focuses on several aspects of morphology and syntax. In contrast to the vocabulary checklist within the CDI-WG, the CDI-WS checklist is limited to language production and asks the parent/guardian to only indicate the words that their child says. The CDI-III consists of three components: 1) a 100 item productive vocabulary checklist, 2) 13 questions about word combinations and; 3) 12 questions about language use.

In terms of norming studies for all the MacArthur-Bates CDIs, data from a group of NH and typically-developing children within the United States of America (USA) was utilised. These norming studies have enabled the CDIs to be utilised for the purpose of evaluating language performance status of individual children relative to their age-matched NH peers. Percentile tables are available in the MacArthur-Bates manual, each of which provides fitted values derived from raw data scores collected from norming studies. Fitted percentile scores are available for various but not all the individual items forming each CDI. For the purposes of this thesis, it was decided that the fitted percentile score (percentile rank) for the productive vocabulary checklist in each CDI would be used for the purpose of assessing language performance in recruited

participants. The parameter of productive vocabulary was chosen for a number of reasons: 1) it is a good representation of language performance in general (A. Jones et al., 2020); 2) it is able to predict other elements of language ability (Marchman & Fernald, 2008); 3) it is reported to be the most robust assessment for children with hearing loss who communicate using sign and/or speech due to accounting for the grammatical differences between signed and spoken languages (Botting et al., 2017), and; 4) it is an item common to all three of the MacArthur-Bates CDIs.

There is large body of evidence to support validity and reliability of both the CDI-WG and CDI-WS when used in typically-developing children (Fenson et al., 2006). These two CDIs have also proven themselves as valid tools for use in children with CIs (Thal et al., 2007). The CDI-III, more recently developed than the other two CDIs, is reported by its authors in their most recent printing of the CDI manual to still be at a relatively early stage of development. Although the validity evidence for the CDI-III is not yet conclusive (Feldman et al., 2005, Oliver et al., 2002), it is sufficiently encouraging to justify its use in the research and clinical setting, which will in turn allow further insight into its indications, fitness for purpose and limitations in both typically-developing NH children and children with CIs.

In addition to the already described limitations of parent-reported measures, the MacArthur-Bates CDIs have their own specific

drawbacks for use in this thesis due to the forms being in American English. However, at the time of designing the methodology for this thesis, no other tool was available that covered such a wide age range. A UK Communicative Development Inventory (UK-CDI) devised by The ESRC International Centre for Language and Communicative Development (LuCiD) was available for use, however this parental questionnaire is only appropriate for children aged 8 to 18 months (LuCiD, 2020). To mitigate for the effect of an American English assessment tool, parents were asked to score their child correctly if their child could say the UK English version of a word where it differed from the American English vocabulary i.e. 'fire engine' instead of 'fire truck' and 'nappy' instead of 'diaper'.

3.6.3.2 The Children's Communication Checklist (CCC-2) – Second Edition

The CCC-2 is a checklist that can be completed by a parent/guardian of a child aged 4 years and over who speaks in simple sentences (Bishop, 2003). It is therefore not suitable for children who are non-verbal or who speak in one- or two-word utterances. The purposes of this communication checklist are: 1) to screen for children who are likely to have a language impairment and require further evaluation by a speech and language therapist; 2) identify pragmatic impairments in children with communication difficulty, and; 3) identify children who may benefit for an assessment for an autism spectrum disorder (ASD) (Bishop, 2003).

The CCC-2 tool consists of 70 multiple choice items that are divided into ten scales, each scale having seven items. Within each scale, five items describe difficulties and two describe strengths. The parent/guardian is asked to rate the frequency with which their child exhibits specific behaviours. The first four scales are often impaired in children with specific language impairment (SLI) and include: i) speech; ii) syntax; iii) semantics, and; iv) coherence. The next four scales cover pragmatic aspects of communication and consist of: v) inappropriate initiation; vi) stereotyped language; vii) use of context, and; viii) nonverbal communication. The final two scales: ix) social relations and x) interests, establish behaviours that are usually impaired in ASD. The General Communication Composite (GCC) is based on the first eight sales and may be used to identify children who are likely to have clinically significant communication problems. Although the CCC-2 can't be used to diagnose ASD, it may help identify children with a communicative profile suggestive of the disorder by providing a Social Interaction Deviance Composite (SIDC). The CCC-2 has been demonstrated as a reliable and valid tool through data acquired from NH clinical samples (Bishop, 2003), and has also been shown to identify communication difficulties when administered to children using CIs (Ramirez-Inscoe & Moore, 2011).

To aid the interpretation of results, raw scores are converted to scaled scores for each item. A scaled score is also provided for the GCC and SIDC. The CCC-2 manual advises that although scaled

scores should be used in research contexts when appropriate i.e. to compare group means, the percentiles should be in the clinical setting. For statistical analysis of data acquired in this thesis, the scaled GCC score was used to evaluate language and communication ability.

In terms of interpretation of scaled scores, the following recommendations are made in the manual: 1) scores at or above the 15th percentile should be regarded as within normal limits; 2) a score around the 10th percentile is not usually concerning if it is seen only on one or two scales, however if more than three scales score below this percentile, it is suggested that a child may warrant further investigation; 3) if two or more scales have scores at or below the 5th percentile, this suggests clinically significant problems with communication; 4) GCC scores below 54, 45 and 40 select the bottom 10%, 5% and 3% respectively; 5) scores below 6th percentile on the social relationships and interests scales in addition to a GCC score below 55 raises the possibility of ASD and a more detailed evaluation by a professional with the relevant expertise is suggested; 6) even if the GCC is within normal limits, a SIDC of $\leq$ -15 is frequently seen in children with ASD and a SIDC $\geq$ 9 is suggestive of a typical specific language impairment.

If an abnormal CCC-2 score (as per the manual recommendations) was detected for a NH participant, prospectively sought parental/guardian consent enabled a researcher to inform the

participant's GP of the result so that an appropriate specialist referral could be made where appropriate. With respect to CI participants, again with parental/guardian consent, either the speech and language therapist of the relevant auditory implant programme or GP was informed depending on whether the participant was still undergoing CI programme follow up.

3.6.4 Parent-Reported Measures of Executive Function Performance

The Behavior Rating Inventory of Executive Function (BRIEF) is the most widely used parent-reported measure of childhood EF (Kronenberger et al., 2020). There are two versions of the BRIEF checklist: 1) The BRIEF-P (Gioia et al., 2003) designed for use in children aged 2 years to 5 years and 11 months, and; 2) The BRIEF-2 (Gioia et al., 2015) that is utilised for children aged 5 to 18 years. In each version, the parent/guardian is asked to rate how often their child has displayed EF related behaviours in the preceding 6 months, with the options being: 1) never; 2) sometimes and; 3) often. Evidence for validity of this tool as a measure of everyday EF is compelling (Roth et al., 2014, Roth et al., 2015) and the experience of its use in children with CIs widely published (Beer et al., 2014; Kronenberger, Beer, et al., 2014; Kronenberger et al., 2020).

The Global Executive Composite (GEC) is a summary score available in both versions of the BRIEF tool that incorporates all clinical scales

of EF. The BRIEF-P consists of five clinical scales: 1) inhibit; 2) shift; 3) emotional control; 4) working memory (WM), and; 5) plan/organise. In addition to these five clinical scales, the BRIEF-2 also includes: 6) self-monitor; 7) initiate; 8) task-monitor, and; 9) organisation of materials. To interpret results, BRIEF-P and BRIEF-2 raw scores need to be converted to *T* scores (based upon an age-based typically-developing normative sample of children from the USA). The *T* scores are linear transformations of the raw scores and have a mean of 50 and a SD of 10 hence, a *T* score of 70 indicates an individual's score is 2 SD's above the normative sample mean. Higher *T* scores indicate less favourable EF. With respect to BRIEF-P, the manual states that a *T* score $\geq$ 65 (for the GEC and all individual subscale scores) should be considered as potentially clinically significant. In terms of the BRIEF-2, the manual states that all *T* scores should be interpreted as follows: i) between 60 and 64 are considered mildly elevated; ii) between 65 and 69 are potentially clinically elevated, and; iii) above 70 are clinically elevated.

For all experiments within this thesis, the BRIEF-P was administered to a parent/guardian of all participants aged 6 months to 4 years and 11 months and the BRIEF-2 to a parent/guardian of all children aged 5 years and older. For the analysis of BRIEF data, *T* scores were used for the GEC result and individual subscales where appropriate. If a participant had a *T* score $\geq$ 65 on the BRIEF-P or $\geq$ 60 on the BRIEF-2, then prospectively gained parental/guardian

consent enabled a researcher to inform the participant's GP of the result (and the relevant auditory implant programme of any CI participant still undergoing follow-up) so that any required specialist referral or management could be organised.

3.7 PARENT-REPORTED MEASURES OF BEHAVIOURAL EXECUTIVE FUNCTION EXPERIMENT

3.7.1 Participants

A group of severe-to-profoundly deaf paediatric CI recipients and a group of hearing children were recruited to this study. Children were recruited to the NH group if their parent/guardian declared there were no known problems with or concerns about their hearing. Common inclusion criteria across the NH and CI groups were:

1) Native English speakers
2) Normal or corrected-to-normal vision
3) Aged between 4 years and 6 years and 11 months
4) Able to talk in simple sentences

Any known cognitive, motor, or language disorder (for example specific language disorder) were defined as exclusion criteria.

3.7.2 Design and Analysis of Data

In this cross-sectional experiment, a parent/guardian of the participant completed both the BRIEF and CCC-2 parent-reported measures. Data acquired from these tools enabled the relationship between EF and language performance to be explored in both NH

children and children with bilateral CIs. The statistical methods used to explore this relationship are described throughout the thesis, but primarily consisted of bivariate linear regression analysis.

3.7.2.1 Determining Sample Size

Ideally this experiment would have been formally powered to detect a statistical relationship between EF and language development in both NH children and CI recipients. However, data from which an estimate of the strength of such a relationship could be derived were lacking for each specific cohort. Although not solely parent-reported measures, one longitudinal study reported the relationship between EF and language skills in a sample of children with a wide range of language abilities at various time points. The correlation between measures of EF and language performance in children aged 4 to 5 years and 5 to 6 years was reported to be r = 0.82 and 0.81 respectively (Gooch et al., 2016).

The G*Power 3.1 statistical power analysis program (Faul et al., 2009) indicated that a sample size of six was required to detect an effect size of 0.81 (Pearson's correlation coefficient r) at an alpha of 0.05 and with 80% power using a bivariate linear regression. However, parent/guardians of 41 NH children and 41 children with CIs responded to the study advert and were therefore recruited to the experiment.

3.8 PERSONAL PROTECTIVE EQUIPMENT FOR COCHLEAR IMPLANT SURGERY EXPERIMENT

To assess the risk of COVID-19 transmission from an infected patient to various HCWs during CI and other mastoid surgery, first an internationally-recognised collaborative research team consisting of academics, engineers, surgeons, anaesthetists and operating theatre staff, objectively assessed the extent of mastoid drilling-induced contamination in a preclinical model and its mitigation via the use of a drape to create a tent over the surgical field. Secondly, an evaluation of various PPE configurations by otologists while performing mastoid drilling on ex-vivo temporal bones was performed. The implementation of recommendations on the PPE and IPC measures required for CI and other mastoid surgery, which developed from the findings of this preclinical study, led to the restart of cochlear implantation at NAIP within NUH NHS Trust. In order to monitor clinical efficacy and safety, the first ten CI and other mastoid surgeries were individually evaluated using a systematic risk-based approach (R. M. Jones et al., 2020).

3.8.1 Preclinical Experiment

As previously discussed in section 2.7.1, the COVID-19 pathogen is potentially transmitted via aerosols (Asadi et al., 2020). Measures that aim to reduce aerosolisation and prevent the spread of mastoid drill-induced dispersion of droplets, bone, blood and tissue had already been somewhat established prior to this preclinical experiment. These IPC measures include the use of single or

multiple drapes to create a tent over the surgical field such as the two-microscope drape method (ENT UK, 2020) and the 'Ototent' (J. X. Chen et al., 2020), amongst others (Carron et al., 2020).

The potential transmission of COVID-19 by aerosols required the PPE solutions evaluated in this study to create an airtight seal around the nasal and oral airways (Tellier et al., 2019). The SARS-CoV-2 virus is also suggested to enter host cells of the human body via ACE2 expression on the conjunctiva and corneal cells of the eye (X. Chen et al., 2020). Unprotected corneas are shown to be at risk of contamination from bone dust and blood particles during mastoidectomy (Hilal et al., 2005). Therefore, an airtight seal was also considered a requirement of any protective eyewear worn during simulated CI surgery in this preclinical experiment. At the time of designing this study, the challenge of combining an operating microscope with ocular PPE had already been emphasised (Philip Clamp, 2020). To address this concern, the evaluation of PPE for CI and other mastoid surgery included a diverse range of potential solutions including full-face masks, and half-face mask and goggle or spoggle (foam-lined goggles) ensembles.

3.8.1.1 Study Design

This study consisted of: 1) an objective assessment of mastoid-drilling induced contamination in a preclinical model, both with and without the use of a drape tent over the surgical field and; 2) a systematic risk-based evaluation (R. M. Jones et al., 2020) of three

PPE configurations by otologists while performing mastoid drilling on ex-vivo temporal bones.

3.8.1.1.1 Objective Assessment of Mastoid-Drill Induced Contamination

CI surgery was simulated in a standard surgical theatre in NUH NHS Trust on human cadaveric temporal bones that, in addition to the temporal bones used in the subsequent preclinical PPE evaluations, were generously provided by Professor Susan Anderson and Dominic Siwek from The School of Life Sciences, University of Nottingham. Mastoid-drill induced contamination onto the operating surgeon and around the surgical field was assessed with and without the use of a drape tent over the surgical field while drilling (ENT UK, 2020). Figure 3.13 shows the experimental set up and floor plan in terms of the position of the surgical drill and the relative locations of various theatre staff, including the operating surgeon, scrub nurse and anaesthetist.

Drilling of the temporal bone, without the microscope, was performed for 1 minute with a drill speed of 60,000 revolutions per minute (rpm). Visualisation of contamination of the surgical field was made possible by replacing the standard drill irrigation fluid with fluorescent dye extracted from glow sticks (Lumistick glow stick®). With the aid of a black light, the extent of contamination was assessed in a darkened operating theatre, and the results photographically documented.

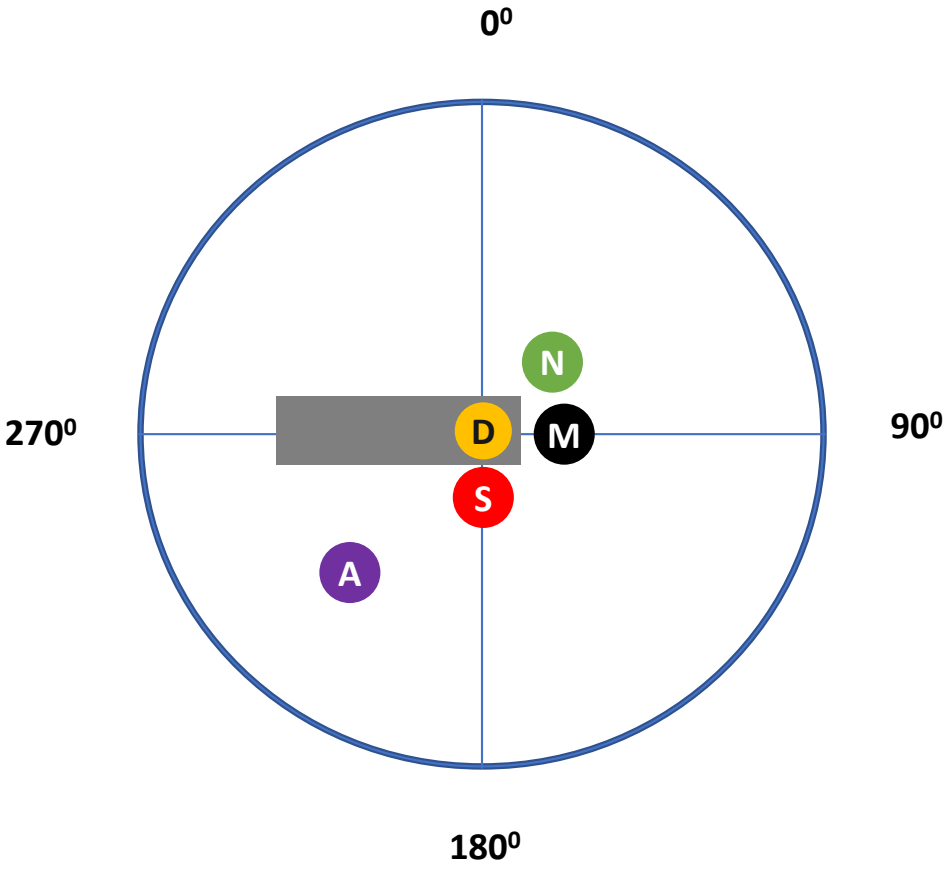


Figure 3.13: Experimental set up and floorplan of the preclinical objective assessment of mastoid-drill induced droplet contamination. The grey rectangle represents the surgical operating table with the drilling position (D) marked upon it. The typical relative positions of the anaesthetist (A), operating surgeon (S), scrub nurse (N) and microscope (M) are also demonstrated.

These steps were subsequently repeated using the two-microscope drape method (ENT UK, 2020) that created a tent over the cadaveric head, hence aimed to reduce the spread of drill induced droplet contamination. In terms of assembly, firstly the surgical microscope (ZEISS OPMI Vario/S88, Jena, Germany) was covered with a standard microscope drape (Glass Lens MICRO-KOVER, Advance Medical Designs, Marietta, USA), which is standard practice for an otology procedure. A second identical standard microscope drape was subsequently attached to the lens of the microscope and

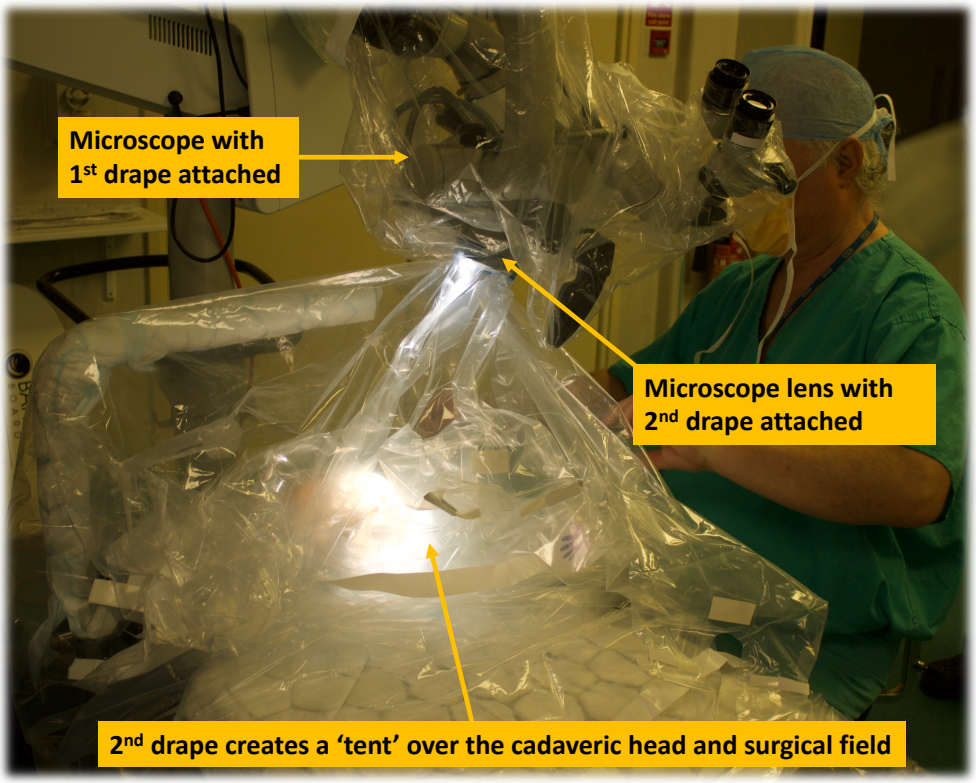


Figure 3.14: The two-microscope drape method (ENT UK, 2020) employed in the preclinical objective assessment of mastoid-drill induced droplet contamination. In terms of set up, the surgical microscope (ZEISS OPMI Vario/S88, Jena, Germany) was covered with a standard microscope drape (Glass Lens MICRO-KOVER, Advance Medical Designs, Marietta, USA). Next, a second identical microscope drape was attached to the lens of the microscope and then pulled down over the surgical field to create a 'tent' over the cadaveric temporal bone.

then pulled down over the surgical field to create a 'tent' over the cadaveric temporal bone (see Figure 3.14).

3.8.1.1.2 Evaluation of Personal Protective Equipment During Simulated Cochlear Implantation

Three PPE configurations were evaluated by otology surgeons while performing mastoid drilling on cadaveric temporal bones (see Figure 3.15): 1) a full-face respirator (Promask; 3M Scott, Munroe, NC, USA; n = 5 otologists); 2) a modified full-face snorkel mask (Pneumask, Stanford, USA; n = 10 otologists), and; 3) the

ensemble of a half-face mask (filtering facepiece [FFP]3 or [FFP]2) and safety goggles or spoggles (n = 5 otologists). The modified full-face snorkel mask is a concept that at the time of writing this thesis was in clinical use across the world (ISINNOVA, 2020; Stanford Bioengineering Prakash Lab, 2020), including within an NHS Foundation Trust in the United Kingdom (Royal Berkshire NHS Foundation Trust, 2020). It consists of a full-face converted snorkel mask, an appropriate medical grade filter that captures viral particles and a custom-made 3D printed adaptor that connects the two. Professor Richard Hague and his colleagues from the faculty of engineering provided the adaptors required for this preclinical experiment through their 3D printing services at The University of Nottingham. The safety goggles (Coverall COVERSI; Bollé, Villeurbanne, France) and safety spoggles (BAXTER BAXPSI foam-lined safety glasses, Bollé, Villeurbanne, France) were chosen as they both meet the safety standards required to protect against liquid droplets or splashed, large dust particles >5μm, and gas and fine dust particles <5μm.

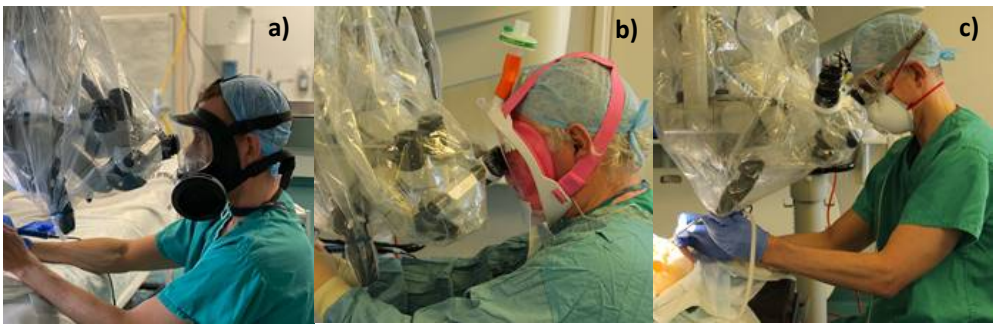


Figure 3.15: The three PPE solutions evaluated during simulated CI surgery. a) full-face respirator (Promask, 3M™ Scott, Monroe, USA); **b)** modified full-face snorkel mask (Pneumask, Stanford, USA) which consists of a full-face mask, an appropriate medical grade filter that captures viral particles, and a custom-made 3D printed adaptor that connects the two; **c)** FFP3 mask (3M™ 1863) and soft goggles (Bollé Coverall COVERSI) or spoggles (Bollé BAXTER RX) used as an ensemble.

As this preclinical experiment was performed during the peak of the first wave of COVID-19, reusable half-face respirators were not routinely available to NUH NHS Trust at the time, hence could not be included in this ergonomic assessment. They were, however, subsequently evaluated in the clinical setting as described in section 3.8.2.

CI surgery was once again simulated in a standard operating theatre with the use of the same surgical microscope (ZEISS OPMI Vario/S88, Jena, Germany) and a cadaveric temporal bone. Study participants were each asked to operate for 30 minutes whilst wearing the various PPE options.

To perform the PPE evaluation, a systematic risk-based approach (R. M. Jones et al., 2020) was implemented and included:

1. Ease of donning and doffing
2. Efficacy of communication
3. Participants' vital physiological parameters including heart rate (HR), oxygen (O_2) saturations, fractional inspired carbon dioxide ($FiCO_2$), and end-tidal carbon dioxide ($ETCO_2$) levels
4. Participants' subjective comfort and breathability levels
5. Participants' visual acuity with and without the microscope and visual fields using the microscope

An ergonomic evaluation of some, but unfortunately not all, of the PPE options over longer periods of time was also performed. As previously mentioned, this study was conducted at the height of the COVID-19 pandemic and the supply of FFP3/2 masks at NUH NHS Trust was limited to use for clinical sessions only. Therefore, this PPE solution could not be subjected to a long-term ergonomic evaluation for the purpose of this research experiment alone. This long-term assessment consisted of all the otologists who participated in the full-face respirator (n = 5) and full-face snorkel mask (n = 10) evaluations wearing the mask at home whilst performing normal day-to-day activities for as long as tolerated. A questionnaire on the usability of each mask over longer periods of time was subsequently completed by these participants. This questionnaire also sought opinions on the efficacy and clinical usability of all types of PPE utilised in this experiment (see 9.1 APPENDIX A: Long term ergonomic PPE questionnaire for otology surgeon participants

Furthermore, qualitative fit testing was performed for all participants who evaluated the full-face respirator (n = 5) and nine of those who trialled the full-face snorkel mask (n = 10). Fit testing was declined by one participant in the full-face snorkel mask group due to concerns over a minor allergic skin reaction. Fit testing was carried out by an appropriately trained administrator and complied with NUH NHS Trust guidelines. The five participants who evaluated the full-face respirator also formed five out of the 10 participants

who underwent the full-face snorkel mask evaluation. Nine out of 10 of the full-face snorkel participants had previously undergone a qualitative fit test for at least one type of FFP3 mask, the result of which was sought from each participant. Qualitative fit testing was not performed for the FFP2 mask, as this was not standard procedure for clinical practice as NUH NHS Trust.

In terms of donning and doffing, NUH NHS Trust guidelines were followed for each type of PPE subjected to a full ergonomic assessment.

Communication was assessed by participants reading lists of monosyllabic words from the Arthur Boothroyd (AB) word test (Boothroyd, 1968) at conversational level in addition to 10 sentences commonly used in theatre such as *'can you pass me the drill?'*. Both the AB word and sentences lists were presented under two conditions: i) with both the drill and suction off (57 dB LAeq average ambient noise level at a distance of 2m), and; ii) with both the drill and suctioned turned on (70 dB LAeq average ambient noise level at a distance of 2m). Both a near listener (located 1.2m from the drill position) and a far listener (located 1.5m from the drill position), simulating the position of a scrub nurse and anaesthetist respectively, were asked to record what they heard. A % correct score was given for the AB words and sentence lists individually, and under each listening condition.

The assessment of vital physiological parameters consisted of taking measurements of HR, O_2 saturations, $FiCO_2$, and $ETCO_2$. HR and O_2 saturation recordings were achieved by attaching a pulse oximeter to the hallux of each participant (on the foot opposite to that used for operating the drill pedal). $FiCO_2$ and $ETCO_2$ measurements were achieved by securing one end of an anaesthetic gas sampling line to each participant's lower face underneath the respirator/face mask (approximately half-way between the upper lip and nostril in line with the corner of the mouth). Both the pulse oximeter and gas sampling line were attached to the anaesthetic machine and for each PPE option, these measurements were continuously monitored and recorded at 5 minute intervals for 30 minutes. Baseline recordings were taken for each physiological parameter for all participants.

Comfort and breathability parameters were recorded at 5 minute intervals whilst participants simulated CI surgery. Participants were asked to subjectively rate each parameter as either good (no perceived effect), adequate (perceived effect but with no effect on performance) or inadequate (perceived effect with detrimental effect on performance).

An objective assessment of visual acuity (without use of the microscope) and the visual field (with the use of the microscope) was also performed for each participant. Visual acuity testing was performed using the Peek Acuity Eye Testing App (Peek Vision

Ltd®) at 0, 15 and 30 minutes (Peek Vision Ltd). For the evaluation of the visual field, participants (n = 5) were asked to draw the outline of their visual field onto a piece of graph paper whilst using the microscope, both with and without PPE.

3.8.2 Clinical Evaluation of Recommended Personal Protective Equipment Following the Resumption of Cochlear Implant Surgery

3.8.2.1 Study Design

The findings of the preclinical study led to recommendations on the required PPE and IPC measures for CI and other mastoid surgery during the COVID-19 pandemic. These recommendations, which consisted of the combination of a FFP3 mask or reusable half-face respirator with safety spoggles as PPE and the use of a drape tent as an additional IPC measure, were implemented by NUH NHS Trust and led to the resumption of CI surgery at NAIP in May 2020. To monitor the clinical efficacy and safety of CI and other mastoid surgery, the first ten cochlear implantation/mastoidectomy cases following the implementation of the PPE and IPC recommendations at NUH NHS Trust were individually evaluated.

Specifically, these ten clinical evaluations consisted of a questionnaire and two objective assessments, which together encompassed the following categories of the systematic risk-based approach to evaluating the recommended PPE and IPC measures (R. M. Jones et al., 2020): 1) donning, doffing and changing; 2)

usability and; 3) fit for purpose. The questionnaire was completed by the operating surgeon and its content is shown in 9.2 APPENDIX B. Five different CI/otology surgeons were involved in the ten evaluations/questionnaires. The exact PPE worn by an individual surgeon was determined by previously performed qualitative fit testing and was compliant with the implemented NUH NHS Trust recommendations for all but one surgeon. One participating surgeon was unable to wear the spoggles due to the requirement for their own personal prescription eyewear. Although it is possible to purchase prescription spoggles (Bollé prescription safety glasses, Villeurbanne, France), they were not available at the time of the CI surgery in this individual case. These ten clinical evaluations were performed later in the first wave of the COVID-19 pandemic compared with the preclinical experiments and because disposable PPE resources such as FFP3 masks were limited and costly, most HCWs had by this point in time been provided with reusable half-face respirators. Hence, most surgeons donned reusable half-face respirators.

In terms of the two objective assessments, the first evaluated donning and doffing of PPE by the surgeon in addition to the identification of any junctions or gaps in the PPE ensemble. The checklist for this assessment adhered to NUH NHS Trust's infection control protocol and was completed by a dedicated 'buddy' who was an appropriate member of the operating theatre team. The second objective assessment evaluated assembly and disassembly of the

utilised drape tent in terms of the additional surgical time required and adherence to published national guidelines (ENT UK, 2020). During a number of these surgical cases, various drapes were used to create the drape tent including a novel commercially designed Nottingham drape tent. The research team hypothesised that this novel design would have advantages over established tent designs and hence improve overall efficiency of CI and other mastoid surgery due to having: i) a CE marking; ii) no requirement for modification during assembly, and; iii) no obstruction to the surgical visual field.

3.8.3 Analysis of Data

Due to the small number of participants in the preclinical study, the acquired quantitative data could not be subjected to robust statistical analysis. Hence, analyses were mainly via descriptive statistics for this experiment. The majority of data in the clinical evaluations were qualitative parameters, hence also reported descriptively.

3.9 CHAPTER SUMMARY

The current chapter has outlined the design and methodology of cross-sectional and longitudinal fNIRS neuroimaging studies conducted to assess behavioural EF-evoked cortical activation within predefined ROIs, in addition to correlates of fronto-temporal connectivity, and how these measures changes over time and with cochlear implantation. As described, parent-reported measures of

EF and language were also acquired in both these experiments. Specific to the longitudinal study, neuroimaging and behavioural data were collected from the same NH children during at least two research appointments, and where possible, these sessions were approximately 12 months apart. The original plan also involved the collection of such data for children with CIs, both pre- and post-implantation at numerous pre-determined time points. However, due to COVID-19, attendance at follow-up research appointments was severely affected, a problem more common amongst the CI participants. The pandemic also had a substantial negative impact on recruitment to both experiments.

However, as detailed throughout this chapter, COVID-19 contingency plans were developed which included preclinical and clinical PPE experiments that enabled CI surgeries to recommence at the primary research site. Investigations into the relationship between EF and language ability continued throughout the COVID-19 induced pause in face-to-face research activity via the parent-reported of behavioural EF experiment. As discussed in upcoming chapters, the data acquired from these parent-reported measures of EF and language, in addition to fNIRS data, were (where appropriate) subjected to robust statistical testing, which enabled the relationship between cortical and behavioural measures of EF and language performance to be formally explored.

4. THE DEVELOPMENT OF BEHAVIOURAL EXECUTIVE FUNCTION

4.1 INTRODUCTION

The current chapter presents behavioural EF task performance data obtained from children with a severe-to-profound SNHL, both pre- and post-implantation, and a group of NH children. The chapter examines the development of these EF abilities over time, and with increasing age in children with and without a SNHL. In keeping with the overall aims of the thesis, the chapter aims to evaluate the level of between-subject variability in EF ability within a population of both typically-developing and deaf children. Unfortunately, due to the adverse impact of COVID-19 on the research testing timeline and the attrition rate associated with the longitudinal fNIRS experiment, the effect of cochlear implantation on the evolution of behavioural EF skills could not be adequately assessed. Data acquired from parent-reported measures of EF is also examined in this chapter, which further facilitates the evaluation of variability in behavioural EF performance amongst both paediatric CI users and NH children.

4.2 ANALYSES

A combination of descriptive statistics and bivariate correlation analysis were used to evaluate performance on all behavioural EF tasks and parent-reported measures of EF. Specifically, bivariate analysis was used to assess for any significant correlation between

age and behavioural EF performance within each group of children. In terms of behavioural EF tasks, some participants within the longitudinal experiment repeated the same task at a later testing session. Therefore, to eliminate learning effect as a confounding factor, only data acquired during a participant's first time performing a specific EF task were included in statistical analysis. Prior to all statistical testing, histograms and the Shapiro-Wilk test were used to examine whether the distribution of each variable significantly differed from normality. The appropriate parametric or non-parametric test was selected accordingly based on whether the variables of interest met the relevant parametric assumptions. The statistical tests utilised are specified in the corresponding sections throughout this chapter.

4.3 RESULTS

4.3.1 Performance on Behavioural Executive Function Tasks

The COVID-19 pandemic severely affected not only recruitment to both the cross-sectional and longitudinal fNIRS studies, but also the original schedule for research testing sessions within the longitudinal experiment (as previously outlined in section 3.4.2.1). Low recruitment to and a high attrition rate from the longitudinal study were observed particularly for the paediatric CI users.

4.3.1.1 Description of Samples

4.3.1.1.1 Paediatric CI Users

In terms of the four participants recruited to the longitudinal fNIRS experiment they were all deemed suitable candidates for cochlear implantation by NAIP. The parents of all participants consented to their child receiving CIs prior to being recruited to the study. Eligibility for implantation was based on whether a child met the National Institute for Health and Care Excellence (NICE) criteria (2019) in addition to an overall assessment of need. The group consisted of two male and two female participants with a mean age of 1.9 years (range 8 months to 3.6 years, SD 1.4 years) at the time of their first testing session. Table 4.1 presents a summary of the clinical characteristics for this sample of CI users. Subjects participating in the longitudinal experiment are identified with the prefix 'CI (LT)' as presented in Table 4.1. All four participants were diagnosed with hearing loss at birth via the NHSP, hence had a pre-lingual deafness. In terms of communication mode, all participants were born into NH families and were being encouraged to develop spoken English language. No participants were reported to use British Sign Language on a regular basis. All participants received a Cochlear™ Nucleus® 6 device (CI622) with Nucleus® 7 (CP1000) sound processor bilaterally. None of the participants experienced any complications during CI surgery or post-operatively. For all participants, no electrodes were located outside of the cochlea on post-operative imaging and post-operative impedances were within

Table 4.1: Summary of clinical characteristics of CI users in the longitudinal fNIRS experiment

a) Participant ID	b) Aetiology of HL	c) Age at HL diagnosis	d) Age at CI Surgery	e) Left HT	f) Right HT	g) Additional Details
CI (LT)_01	Connexin 26 mutation	Birth – Detected at NHSP	3.8 years	85	84	Met CI candidacy criteria at 3.2 years following revision of NICE guidance in March 2019
CI (LT)_02	Unknown	Birth – Detected at NHSP	9 months	95	100	-
CI (LT)_03	Unknown	Birth – Detected at NHSP	2.4 years	82	85	SNHL progressive, hence met CI candidacy criteria at an older age
CI (LT)_04	Unknown	Birth – Detected at NHSP	13 months	105	110	-

Column **a)** Participant ID; **b)** Aetiology of hearing loss; **c)** Age at diagnosis of bilateral hearing loss; **d)** Age at time of CI surgery; **e)** Average unaided hearing threshold (dB) for left ear across 0.5, 1, 2, 3 & 4 kHz; **f)** Average unaided hearing threshold (dB) for right ear across 0.5, 1, 2, 3 & 4 kHz; **g)** Additional relevant clinical details.

normal range for all electrodes. All participants had their devices activated at four weeks post-operatively, with comfort and threshold levels estimated for each electrode position by the clinical team according to standard clinical protocols. Prior to cochlear implantation, all participants regularly wore bilateral hearing aids (HAs).

Following the COVID-19 pandemic, it was necessary to amend the original testing schedule from that outlined in section 3.4.2.1. The study's actual testing timeline is provided in Figure 4.1. Session T0 took place at the participant family's earliest convenience before undergoing CI surgery. The pause in face-to-face research activity at NUH NHS Trust extended from mid-march 2020 until mid-December 2020. As soon as UK government guidance allowed face-to-face research activity to recommence, every effort was made to arrange testing sessions for all recruited participants. Despite these efforts, only two CI participants underwent a second testing session (still referred to as T1). For participant CI (LT)_01, the T1 session took place 29 days after CI activation. Participant CI (LT)_02 had a significantly delayed T1 session, which occurred 13 months after CI activation.

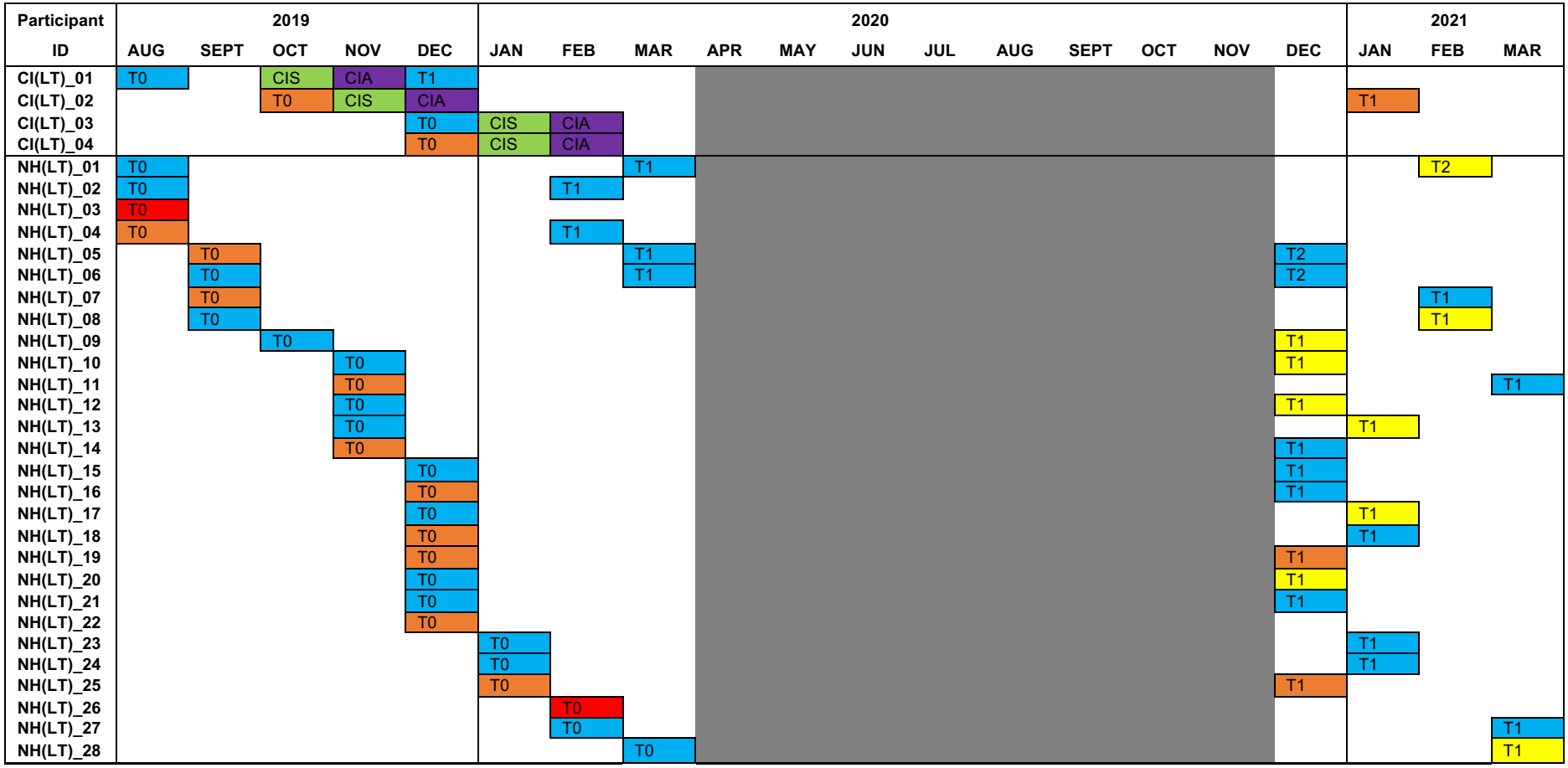


Figure 4.1: Recruitment and testing timeline for all fNIRS study participants. T0, T1 and T2 denote the month in which the 1st, 2nd and 3rd testing sessions took place respectively. The executive function task performed at each testing session is indicated by colour; orange = A-not-B task; blue = tongue and mommy/me tasks; yellow = Go/NoGo and N-back tasks. If a participant refused to perform an executive function task at a session, this is indicated by the colour red. CI surgery and device activation are denoted as 'CIS' and 'CIA' respectively. The shaded grey area indicates the 9 month pause in face-to-face research activity.

Family circumstances had prevented the attendance of participant CI (LT)_02 at their originally scheduled T1 session and the subsequent pandemic delayed their ability to return for testing until January 2021.

The pandemic also understandably led to a high attrition rate. Participants CI (LT)_01, CI (LT)_03 and CI (LT)_04 all withdrew from the study prior to its formal closure. The parents of all these participants explained the reason for withdrawal as an inability to travel to Nottinghamshire during COVID-19 for further testing sessions. Further details of missed testing sessions (in addition to those missed sessions for NH participants) are presented in Table 4.2. As CI (LT)_02 had their T1 session 13 months after CI activation, no further testing sessions were performed for this participant as the original pre-COVID plan was to perform the final testing session approximately 12 months after CI activation. Table 4.3 gives further details about the completed testing sessions including the age of participants at each session and the tasks performed.

As data acquired from the fNIRS cross-sectional experiment is also discussed in this section, the characteristics of the two CI users recruited to this study are outlined in Table 4.4. Participant IDs for this cohort include the prefix 'CI (CS)'. The behavioural Go/NoGo and N-back tasks were administered to both these participants during a single testing session, although CI (CS)_01 refused to

Table 4.2: Summary of missed testing sessions for participants in the longitudinal fNIRS experiment

Group	Testing Session	Number of Participants Missing Session	Reason(s) for Missed Sessions
CI (LT)	T0	0 (n = 4)	-
CI (LT)	T1	2 (n = 4)	CI (LT)_03 & CI (LT)_04 withdrew participation prior to a T1 session.
CI (LT)	T2	4 (n = 4)	CI (LT)_01 withdrew participation prior to a T2 session. Due to the impact of COVID-19 on the testing timeline, CI (LT)_02 did not undergo a T2 session.
CI (LT)	T3	4 (n = 4)	Due to the impact of COVID-19 on the testing timeline, CI (LT)_02 did not undergo a T3 session.
NH (LT)	T0	0 (n = 28)	-
NH (LT)	T1	3 (n = 28)	NH (LT)_03, NH (LT)_22 & NH (LT)_26 withdrew participation prior to a T1 session.
NH (LT)	T2	25 (n = 28)	Due to impact of COVID-19 on the testing timeline, only NH (LT)_01, NH (LT)_05 & NH (LT)_06 underwent a T2 session.

CI (LT) and **NH (LT)** denote CI user and NH participants recruited to the longitudinal experiment respectively.

Table 4.3: Summary of testing sessions completed by CI users in the longitudinal fNIRS experiment

a) Participant ID	b) Testing Sessions	c) Age at T0	d) EF Task at T0	e) Listening Devices at T0	f) Age at T1	g) EF Task at T1	h) Listening Devices at T1	i) T0 - T1 Interval	j) Age at BRIEF	k) BRIEF Version
CI (LT)_01	2	3.6 years	Tongue & Mommy/Me	Bilateral HAs	3.9 years	Tongue & Mommy/Me	Bilateral CIs	4 months	4.9 years	BRIEF-P
CI (LT)_02	2	8 months	A-not-B	Bilateral HAs	23 months	A-not-B	Bilateral CIs	15 months	24 months	BRIEF-P
CI (LT)_03	1	2.3 years	Tongue & Mommy/Me	Bilateral HAs						
CI (LT)_04	1	12 months	A-not-B	Bilateral HAs						

Column **a)** Participant ID; **b)** Number of testing sessions attended; **c)** Age at first testing session (T0); **d)** Executive function (EF) task performed at first testing session (T0); **e)** Listening devices used at first testing session (T0); **f)** Age at second testing session (T1); **g)** EF task performed at second testing session (T1); **h)** Listening devices used at second testing session (T1); **i)** Time interval between first (T0) and second (T1) testing session; **j)** Age at completion of BRIEF parent-reported measure; **k)** BRIEF version completed. Grey shaded area represents lack of data.

Table 4.4: Summary of characteristics of CI users in the cross-sectional fNIRS experiment

a) Participant ID	b) Aetiology of HL	c) Age at HL diagnosis	d) Age at CI Surgery	e) Age at Testing Session	f) Age at BRIEF	g) BRIEF Version	h) Additional Details
CI (CS)_01	X linked deafness (*POU3F4* mutation)	Birth – Detected at NHSP	4.4 years	6.6 years	6.6 years	BRIEF-2	SNHL progressive in nature, hence met CI candidacy criteria at an older age
CI (CS)_02	Unknown	Diagnosed at 2.5 years	3.0 years	4.3 years	4.3 years	BRIEF-P	Passed NHSP, but later diagnosed with profound SNHL at 2.5 years

Column **a)** Participant ID; **b)** Aetiology of hearing loss; **c)** Age at diagnosis of hearing loss; **d)** Age at CI surgery; **e)** Age at testing session; **f)** Age at completion of parent-reported BRIEF; **g)** Version of BRIEF completed; **h)** Relevant additional details.

perform the N-back task. Both participants were recruited via the Midlands Hearing Implant Programme and previously received a Cochlear™ Nucleus® 6 device (CI622) with Nucleus® 7 (CP1000) sound processor bilaterally.

4.3.1.1.2 NH Children

The twenty-eight NH participants recruited to the fNIRS longitudinal experiment (indicated with the prefix 'NH (LT)') comprised 17 males and 11 females with a mean age of 2.3 years (range 8 months to 3.7 years, SD = 0.97 years) at the time of recruitment. A summary of the characteristics of these subjects, in addition to the behavioural tasks they performed at each session is presented in Table 4.5. Like the CI group, the testing timetable was adversely impacted by COVID-19, with most participants having only two research sessions. As presented in Table 4.6, the mean retest interval between the first (T0) and second (T1) research session was 11.57 months. Unfortunately, the research timeline allowed only three NH participants in the longitudinal experiments to have a third (T2) testing session. Attrition was less of a problem for the NH group compared with CI users as highlighted in Table 4.2.

This section also includes data acquired from NH participants recruited to the cross-sectional fNIRS experiment (indicated with the prefix 'NH (CS)'), hence the characteristics of these subjects are presented in Table 4.7.

Table 4.5: Summary of characteristics of NH participants in the longitudinal fNIRS experiment

a) Participant ID	b) Testing Sessions	c) Age at T0	d) EF Task at T0	e) Age at T1	f) EF Task at T1	g) Age at T2	h) EF Task at T2	i) Age at BRIEF
NH (LT)_01	3	2.8	T & M	3.4	T & M	4.3	G & N	4.0
NH (LT)_02	2	2.1	T & M	2.6	T & M			3.1
NH (LT)_03	1	3.2	Refused					
NH (LT)_04	2	19 months	A-not-B	2.0	T & M			2.7
NH (LT)_05	3	20 months	A-not-B	2.2	T & M	3.0	T & M	2.8
NH (LT)_06	3	2.6	T & M	3.1	T & M	3.8	T & M	3.6
NH (LT)_07	2	12 months	A-not-B	2.4	T & M			2.1
NH (LT)_08	2	3.4	T & M	4.8	G & N			4.5
NH (LT)_09	2	3.3	T & M	4.3	G & N			4.3
NH (LT)_10	2	3.0	T & M	4.0	G & N			4.0
NH (LT)_11	2	8 months	A-not-B	2.1	T & M			
NH (LT)_12	2	3.1	T & M	4.2	G & N			4.1
NH (LT)_13	2	3.7	T & M	4.8	G & N			4.8
NH (LT)_14	2	22 months	A-not-B	2.9	T & M			2.8
NH (LT)_15	2	2.4	T & M	3.4	T & M			3.4
NH (LT)_16	2	22 months	A-not-B	2.8	T & M			2.8
NH (LT)_17	2	3.3	T & M	4.4	G & N			4.3
NH (LT)_18	2	12 months	A-not-B	2.1	T & M			2.1
NH (LT)_19	2	8 months	A-not-B	20 months	A-not-B			*
NH (LT)_20	2	3.6	T & M	4.6	G & N			4.7
NH (LT)_21	2	2.0	T & M	3.0	T & M			3.0
NH (LT)_22	1	11 months	A-not-B					
NH (LT)_23	2	2.7	T & M	3.7	T & M			3.7
NH (LT)_24	2	2.0	T & M	3.0	T & M			3.0
NH (LT)_25	2	11 months	A-not-B	22 months	A-not-B			*
NH (LT)_26	1	3.2	Refused					
NH (LT)_27	2	2.4	T & M	3.4	T & M			3.5
NH (LT)_28	2	3.4	T & M	4.4	G & N			4.5

Column **a)** Participant ID; **b)** Number of testing sessions attended; **c)** Age at first testing session (T0); **d)** Executive function (EF) task at first testing session (T0), T&M denotes Tongue and Mommy/Me tasks. NH (LT)_03 & NH (LT)_26 both refused to perform an EF task; **e)** Age at second testing session (T1); **f)** EF task at second testing session (T1), G&N denotes Go/NoGo and N-back tasks; **g)** Age at third testing session (T2); **h)** EF task at third testing session (T2); **i)** Age at completion of BRIEF parent-reported measure (BRIEF version was BRIEF-P for all participants), *indicates participant too young for BRIEF. Grey shaded area represents lack of data. N.B. Age is in years for all columns unless otherwise stated.

Table 4.6: Summary of retest interval durations

Group	T0 - T1 Retest Interval (months)	T1 - T2 Retest Interval (months)
NH (LT)	11.57 (3.10)	10.0 (0.69)
CI (LT)	9.5 (7.8)	

Mean (SD) retest interval duration between the first (T0) and second (T1) testing session for both groups of participants in the longitudinal experiment, and between the second (T1) and third (T2) testing sessions for the NH participants. Grey shaded area represents lack of data.

Table 4.7: Summary of characteristics of NH participants in the cross-sectional fNIRS experiment

Participant ID	Age at Research Session (years)	Age at BRIEF (years)	BRIEF Version
NH (CS)_01	4.4	4.4	BRIEF-P
NH (CS)_02	5.4	5.4	BRIEF-2
NH (CS)_03	4.2	4.2	BRIEF-P
NH (CS)_04	5.3	5.3	BRIEF-2
NH (CS)_05	4.8	4.8	BRIEF-P
NH (CS)_06	4.9	4.9	BRIEF-P
NH (CS)_07	6.3	6.3	BRIEF-2
NH (CS)_08	4.0	4.0	BRIEF-P
NH (CS)_09	6.0	6.0	BRIEF-2
NH (CS)_10	5.9	5.9	BRIEF-2
NH (CS)_11	4.6	4.6	BRIEF-P
NH (CS)_12	6.8	6.8	BRIEF-2
NH (CS)_13	4.9	4.6	BRIEF-P
NH (CS)_14	6.0	5.7	BRIEF-2
NH (CS)_15	6.0	6.0	BRIEF-2
NH (CS)_16	6.2	5.9	BRIEF-2
NH (CS)_17	5.2	4.9	BRIEF-P
NH (CS)_18	5.0	4.7	BRIEF-P

4.3.1.2 Performance on A-not-B Task

Ten NH and two CI participants within the longitudinal fNIRS experiment performed the A-not-B task (as outlined in Tables 4.3 and 4.5). Two of the NH participants and one CI user repeated this task at their second testing session. Performance on the A-not-B task for each participant as a function of chronological age is displayed in Figures 4.2 and Figure 4.3. Figure 4.2 details performance in terms of % correct trials. Participants did not necessarily perform the same number of trials in this task, hence Figure 4.3 reflects the task performance level achieved according to the scale outlined in Table 3.1 (see Section 3.4.3.2.1). For those participants who repeated the A-not-B task, interpolation lines have been fitted to demonstrate individual subject performance over time.

Despite the small sample size, several NH participants were the same age (born within the same month) as each other when performing the A-not-B task. Visual inspection of the scatterplots in Figures 4.2 and 4.3 demonstrates a substantial level of between-subject variability for NH participants of the same age, perhaps more so for the performance level reached than the % correct trials. Individual trajectories showed that all participants who repeated the task improved their performance over time. Due to a sample size of two, it is difficult to draw conclusions on task performance in the CI group. Nonetheless, the CI participant who performed two A-not-B

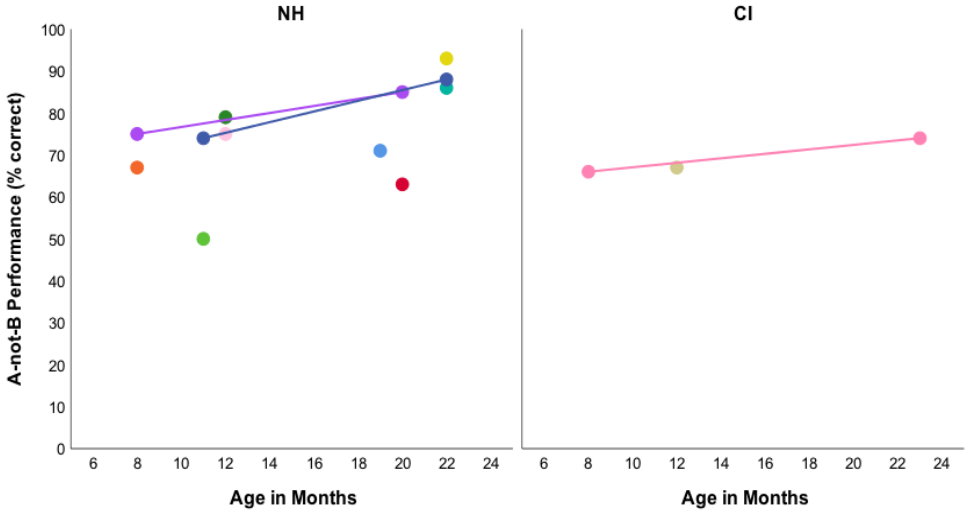


Figure 4.2: Scatterplot to demonstrate performance on A-not-B task (percentage of correct trials) as a function of age for participants in the NH (n = 10) and CI (n = 2) groups. Data points are colour coded by participant and interpolation lines indicate individual trajectories of performance. For the CI participant who repeated the task (pink data points), the A-not-B task was performed both pre- and post- cochlear implantation. The other participant in the CI group performed the A-not-B task pre-implantation only.

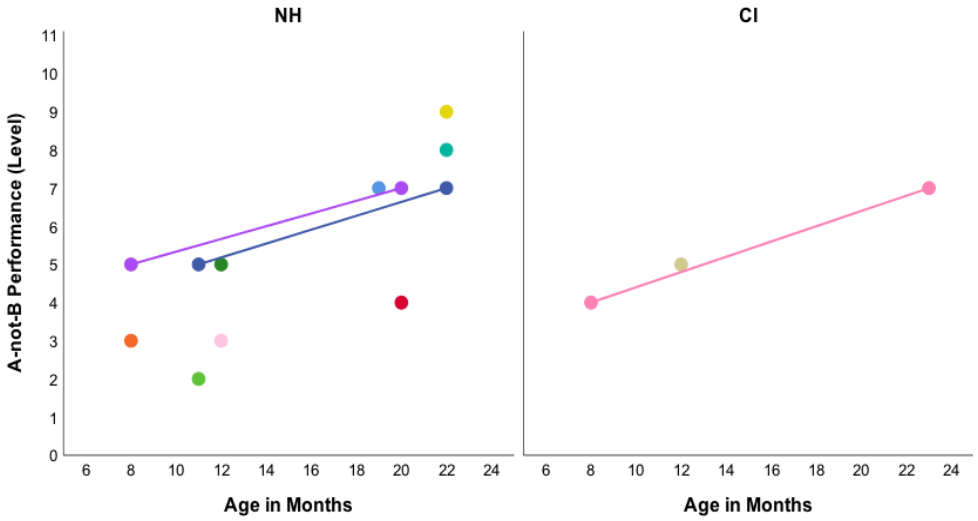


Figure 4.3: Scatterplot to demonstrate performance on A-not-B task (performance level) as a function of age for participants in the NH (n = 10) and CI (n = 2) groups. Data points are colour coded by participant and interpolation lines indicate individual trajectories of performance. For the CI participant who repeated the task (pink data points), the A-not-B task was performed both pre- and post- cochlear implantation. The other participant in the CI group performed the A-not-B task pre-implantation only. Performance level on the A-not-B task was determined according to the scale outlined in section 3.4.3.2.1.

sessions had a trajectory of improvement in performance level that was like that of the two NH participants (Figure 4.3). Although, the two NH subjects did reach an equivalent task performance level at a younger age than this CI user. Bivariate correlation analysis in NH participants (Kendall's tau-b correlation coefficient, T_b) revealed no evidence of an association between age and A-not-B performance in terms of both % correct (T_b =.33, p =.20, 2-tailed) and performance level (T_b =.51, p =.052, 2-tailed). Therefore, despite the observation that individual performance improved over time in the two NH subjects and one CI user that repeated the A-not-B task, age did not correlate with A-not-B performance level at the group level in NH participants. Due to the limited sample size, similar analysis could not be performed for the CI cohort.

4.3.1.3 Performance on Tongue & Mommy/Me Tasks

Twenty-three NH and two CI participants within the longitudinal experiment performed the tongue and mommy/me tasks during at least one testing session. Nine of the NH participants and one CI user repeated both these tasks at a second testing session, and one NH participant once again performed each task at a third testing session. Performance on the tongue and mommy/me tasks for each participant as a function of age is displayed in Figures 4.4 and Figure 4.5 respectively. As each participant completed the same number of trials for each task, only performance in terms of % correct trials is analysed.

4.3.1.3.1 Tongue Task

Substantial between-subject variability was observed for performance on the tongue task amongst NH participants of an extremely similar age. For example, performance ranged from 11 to 100% correct in two children aged only two months apart. Individual trajectories show most NH subjects improved their performance over time, however two children performed less favourably at their second testing session. Although only two CI participants from the CI group performed this task, performance was $\geq$ 90% correct for both subjects.

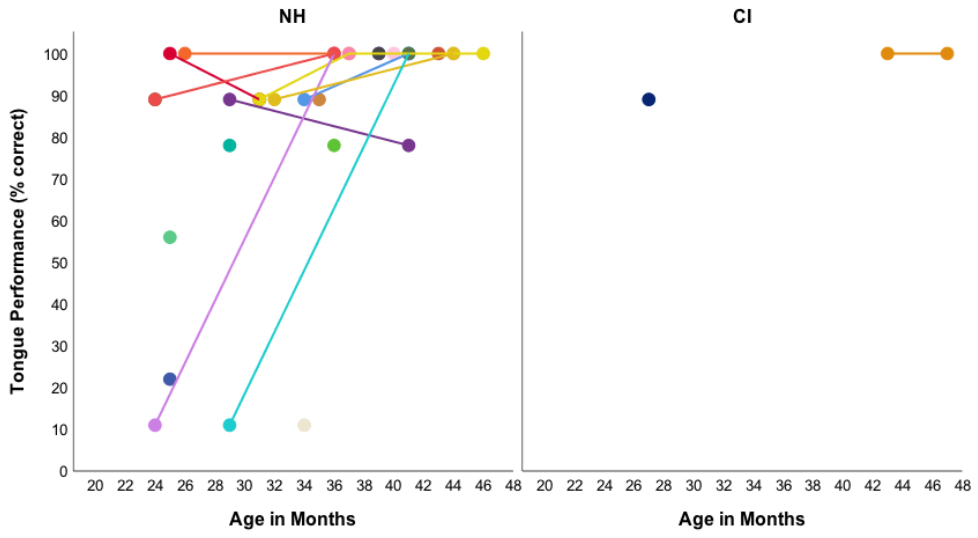


Figure 4.4: Scatterplot to demonstrate performance on tongue task (percentage of correct trials) as a function of age for participants in the NH (n = 23) and CI (n = 2) groups. Data points are colour coded by participant and interpolation lines indicate individual trajectories of performance. For the CI participant who repeated the task (orange data points), the tongue task was performed both pre- and post-cochlear implantation. The other participant in the CI group performed the tongue task pre-implantation only.

Once aged $\geq$ 43 months, all participants in both groups performed at ceiling level. Bivariate correlation analysis in NH participants revealed that performance on the tongue task was significantly positively correlated with age (T_b =.46, p < .05, 2-tailed) at the group level. Due to the limited sample size, similar analysis could not be performed for the CI cohort.

4.3.1.3.2 Mommy/Me Task

Like the tongue task, performance on the mommy/me task was extremely variable in NH children. Substantial between-subject variability was observed even amongst children who differed in age by less than a month, with performance ranging from 0 to >90% correct in such children. Four NH participants performed at ceiling, however one of these participants had performed the task at two previous testing sessions so performance in this subject may have been associated with a learning effect. Twelve NH participants performed at floor level. Most participants who performed the task at more than one testing session improved their performance over time, including the CI user who performed the task both pre- and post-implantation. However, performance for three NH participants remained at 0% correct at a second testing session. Bivariate correlation analysis in NH participants revealed that task performance was significantly positively correlated with age (T_b =.50, p < .05, 2-tailed) at the group level.

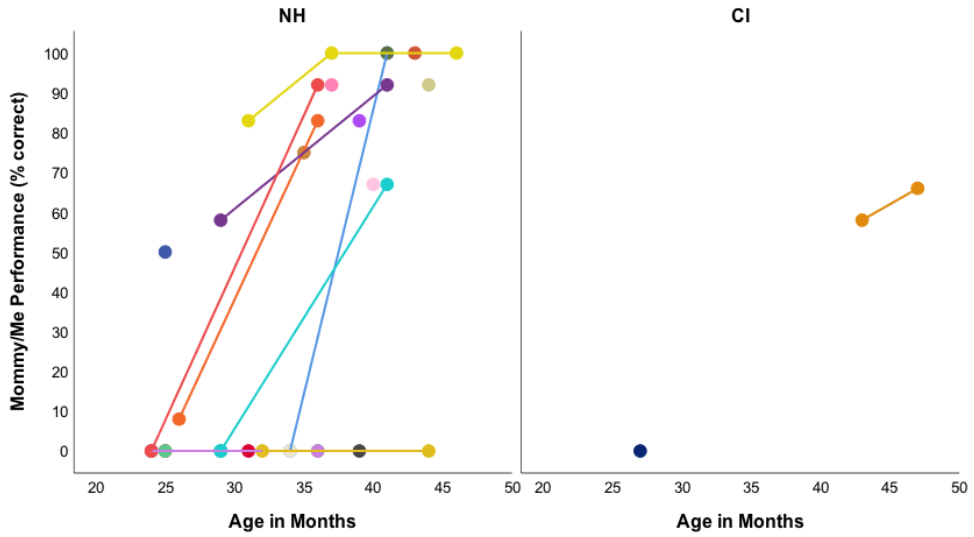


Figure 4.5: Scatterplot to demonstrate performance on mommy/me task (percentage of correct trials) as a function of age for participants in the NH (n = 23) and CI (n = 2) groups. Data points are colour coded by participant and interpolation lines indicate individual trajectories of performance. For the CI participant who repeated the task (orange data points), the mommy/me task was performed both pre- and post- cochlear implantation. The other participant in the CI group performed the mommy/me task pre-implantation only.

4.3.1.4 Performance on Go/NoGo & N-Back Tasks

Twenty-seven NH and two CI participants were allocated the Go/NoGo and N-back tasks at a single testing session. These included participants from both the cross-sectional and longitudinal fNIRS experiments as outlined in Table 4.8. Table 4.8 also provides details on the missing data for each task according to group. Performance on Go/NoGo and N-back tasks as a function of age is shown in Figures 4.6 and 4.7 respectively. Visual inspection of the scatter plots reveals substantial between-subject variability in performance on both tasks for NH subjects of extremely similar ages, an observation more apparent for the Go/NoGo task. Unfortunately, once again, the extremely limited sample size for CI users prevented similar analysis in this cohort.

Table 4.8: Summary of participants performing the Go/NoGo and N-back tasks and the missing data for each task

a)	b)	c) Missing Data	
Group	**Number Participants**	**Go/NoGo**	**N-back**
NH (LT)	9	1	1
NH (CS)	18	0	1
TOTAL	**27**	**1**	**2**
CI (LT)	0	-	-
CI (CS)	2	0	1
TOTAL	**2**	**0**	**1**

Column **a)** Participant group; **b)** Number of participants allocated to each group; **c)** Missing data for each task according to participant group. Computer equipment failure resulted in loss of Go/NoGo and N-back task data in one NH (LT) participant. One NH (CS) participant and one CI (CS) participant refused to attempt the N-back task.

Across the full age range of children performing this task (4.0 to 6.8 years), overall mean accuracy in terms of dPRIME was 2.01 (SD 1.50) for the Go/NoGo task and 2.49 (SD 1.05) for the N-back task. Bivariate correlation analysis in NH participants revealed that task performance was significantly positively correlated with age (T_b =.35, p <.05, 2-tailed) for the N-back task. Conversely, performance on the Go/NoGo task was not associated with age at the group level (T_b =.23, p = .11, 2-tailed).

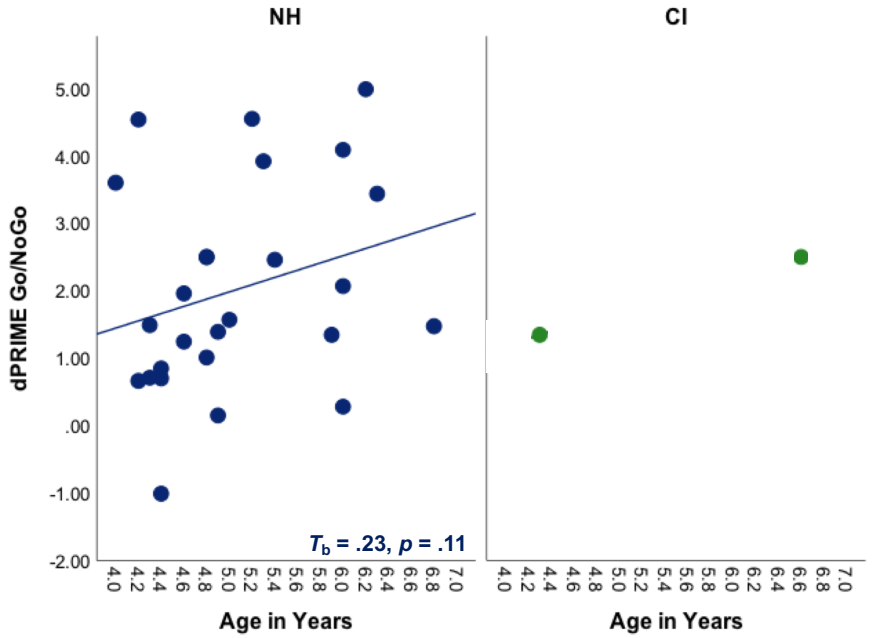


Figure 4.6: Scatterplot to demonstrate performance accuracy (dPRIME) on the Go/NoGo task as a function of age for participants in the NH (n = 26) and CI (n = 2) groups with the regression line shown for NH participants. Increasing dPRIME score denotes increasing accuracy of task performance.

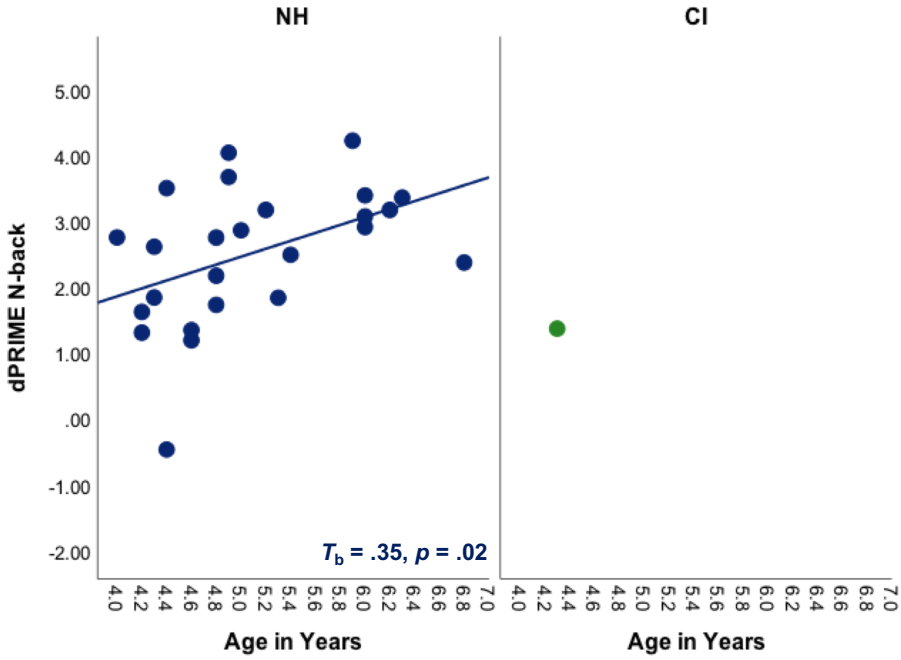


Figure 4.7: Scatterplot to demonstrate performance accuracy (dPRIME) on the N-back task as a function of age for participants in the NH (n = 25) and CI (n = 1) groups with the regression line shown for NH participants. Increasing dPRIME score denotes increasing accuracy of task performance.

4.3.2 Parent-Reported Measures of Behavioural Executive Function

4.3.2.1 Description of Samples

The BRIEF tool was used to acquire parent-reported measures of EF in all NH and CI participants aged over 2.0 years (subject to participant attrition). The BRIEF-P version was used for children aged between 2.0 and 4.9 years, and the BRIEF-2 for children aged between 5.0 and 6.9 years. Parent-reported measures of EF were acquired across the cross-sectional and longitudinal fNIRS experiments in addition to the dedicated parent-reported measures of EF experiment (as described in section 3.7). Table 4.9 outlines the number of NH and CI participants for which BRIEF-P and BRIEF-2 data was acquired. Table 4.10 outlines the characteristics of the participants recruited to the dedicated parent-reported measures of EF experiment.

Table 4.9: Summary of participants for who measures of parent-reported measures of EF were acquired and the version of BRIEF employed

	BRIEF-P	BRIEF-2
Group	**Number of Participants**	**Number of Participants**
NH (LT)	22	0
NH (CS)	7	6
NH (PRM)	15	26
NH TOTAL	**44**	**32**
CI (LT)	2	0
CI (CS)	1	1
CI (PRM)	17	24
CI TOTAL	**20**	**25**

PRM denotes participants recruited to the dedicated parent-reported measures experiment.

Table 4.10: Summary of characteristics of NH children and paediatric CI users recruited to the parent-reported measures experiment

a) Group	b) Number of Participants	c) Aetiology of HL	d) Age at HL diagnosis	e) Age at CI Surgery	f) Age at BRIEF	g) BRIEF Version
CI (PRM)	41	Unknown (n = 20) Connexin 26 mutation (n = 13) Pendred syndrome (n = 5) Auditory neuropathy (n = 2) MYO15A mutation (n = 1)	Birth – Detected at NHSP (n = 33) 2 months (n = 2) 4 months (n = 2) 11 months (n =1) 13 months (n = 2) 2.5 years (n = 1)	Mean = 21.1 months (SD 16.03) Range = 5 months - 6 years	Mean = 5.4 years (SD 0.95) Range 4.1 - 6.9 years	BRIEF-P (17) BRIEF-2 (24)
NH (PRM)	41	-	-	-	Mean = 5.4 years (SD 0.83) Range = 4.1 - 6.9 years	BRIEF-P (15) BRIEF-2 (26)

Column **a)** Participant group (PRM = Dedicated parent-reported measures group); **b)** Number of participants in each group; **c)** Aetiology of hearing loss, number of participants affected by each aetiology in parentheses; **d)** Age at diagnosis of hearing loss, number of participants of respective age in parentheses; **e)** Age at insertion of CI device; **f)** Age when BRIEF performed; **g)** Number of participants performing each version of the BRIEF tool, number in parentheses. SD denotes standard deviation.

4.3.2.2 Performance on The BRIEF Global Executive Composite (GEC)

As outlined in section 3.6.4, the Global Executive Composite (GEC) is the summary score that incorporates all five clinical scales of the BRIEF-P and all nine clinical scales of the BRIEF-2. Performance on the BRIEF-P and BRIEF-2 for each participant, in terms of GEC *T* score, as a function of age is displayed Figures 4.8 and 4.9 respectively. Higher scores on both versions of BRIEF represent less favourable EF performance. As shown in Figure 4.8, bivariate correlation analysis revealed no evidence of an association between age and BRIEF-P performance in either NH children (T_b =-.09, p =.40, 2-tailed) or paediatric CI users (T_b =-.13, p =.44, 2-tailed). Furthermore, as demonstrated in Figure 4.9, bivariate correlation analysis (Pearson's correlation coefficient, r) revealed no association between age and BRIEF-2 performance in either the NH (r =.31, p =.09, 2-tailed) or CI group (r =.15, p =.45, 2-tailed). Whilst Figure 4.9 shows a trend towards higher BRIEF scores (hence worsening EF) with increasing age, this trend did not reach statistical significance for either participant group.

In terms of BRIEF-P, four NH and three CI participants had an abnormally elevated GEC *T* score of potential clinical significance. With respect to BRIEF-2 and NH participants, three subjects had a mildly elevated score and one subject had a potentially clinically elevated score. Interestingly, within the CI user group, three participants had a mildly elevated score, four had a potentially clinically elevated score and seven had a clinically elevated score.

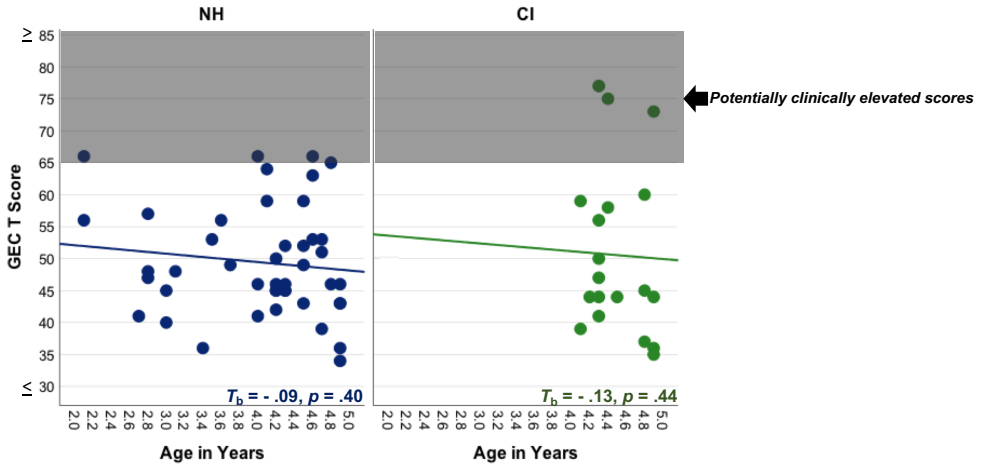


Figure 4.8: Scatterplot to demonstrate performance on the BRIEF-P as a function of age for participants in the NH (n = 44) and CI (n = 20) groups with the regression line shown. A GEC *T* score of 50 represents the mean of the *T* score distribution for the normative BRIEF-P sample (according to the BRIEF-P user manual). A *T* score of 65 represents 1.5 standard deviations above the mean, which is the recommended threshold for interpretation of a score as abnormally elevated. This area of potential clinical significance is indicated by the grey shaded area.

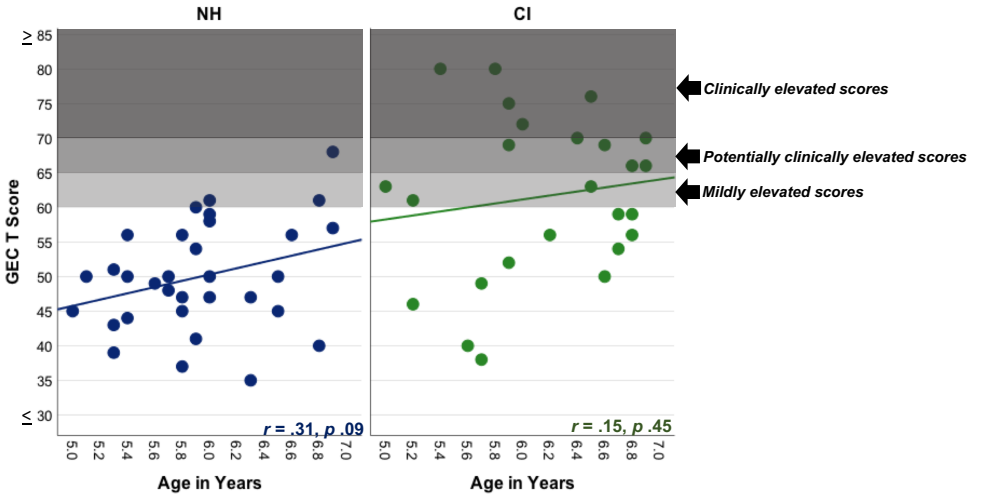


Figure 4.9: Scatterplot to demonstrate performance on the BRIEF-2 as a function of age for participants in the NH (n = 32) and CI (n = 25) groups with the regression line shown. A GEC *T* score of 50 represents the mean of the *T* score distribution for the normative BRIEF-2 sample (according to the BRIEF-2 user manual). The lightly shaded grey area between *T* scores of 60 and 64 represent scores between 1 and 1.5 standard deviations (SDs) above the mean and indicates mildly elevated scores; the next grey shaded area between *T* scores of 65 and 69 represents scores between 1.5 and 2 SDs above the mean and indicates potentially clinically elevated scores and; *T* scores above 70 represent 2 SDs above the mean which is the recommended threshold for interpretation of a score as clinically elevated.

An independent *t*-test revealed no significant difference in the BRIEF-P GEC *T* score for NH participants (mean = 49.43, SD 8.5) compared with CI users (mean = 50.7, SD 12.8), $t(62) = -4.68$, $p = .66$) (2-tailed). Interestingly, a separate independent *t*-test revealed CI users to have significantly higher BRIEF-2 GEC *T* scores (mean = 61.56, SD = 11.6) compared with NH participants (mean = 49.97, SD 7.7), $t(40) = 4.49$, $p<.001$ (2-tailed).

Visual inspection of the scatterplots in Figures 4.8 and 4.9 demonstrates substantial between-subject variability in BRIEF GEC *T* scores amongst participants of extremely similar, and in some cases, the same age in both the NH and CI groups. Figures 4.10 and 4.11 show the mean *T* scores for the BRIEF individual clinical scales for all those participants that had either a potentially clinically elevated or clinically elevated GEC *T* score (score $\geq$ 65) on BRIEF-P (NH n = 4, CI n = 3) and BRIEF-2 (NH n = 1, CI n = 11) respectively. In terms of BRIEF-P, CI users exhibited potentially clinically elevated scores across all individual clinical scales on BRIEF-P, with the highest mean score observed for working memory (WM). For NH participants, the highest mean score was observed for the plan/organize clinical scale. With respect to BRIEF-2, CI users displayed clinically elevated mean scores on the shift and emotional control clinical scales. This group also exhibited potentially clinically elevated scores on the inhibit clinical scale, as did the one NH participant who also displayed an elevated score on the shift scale. The mean age at cochlear implantation for the CI users with

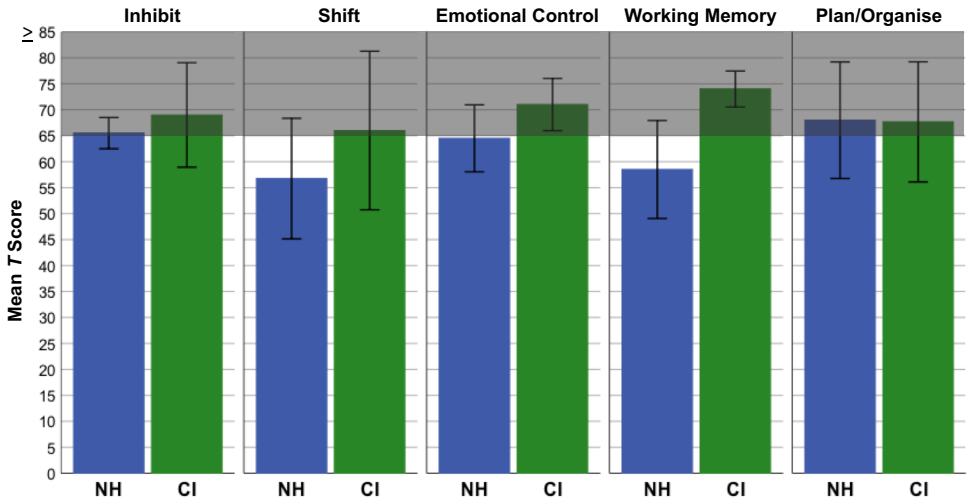


Figure 4.10: Mean *T* scores for the individual clinical scales of those NH (n = 4) and CI (n = 3) participants who had elevated GEC *T* scores on the BRIEF-P. A *T* score of 65 on each clinical scale represents 1.5 standard deviations (SDs) above the mean of the *T* score distribution for the normative BRIEF-P sample (according to the BRIEF-P user manual). Hence, the grey shaded area represents potentially clinically elevated scores for each individual clinical scale. Error bars represent ± 1 standard error of the mean (SEM).

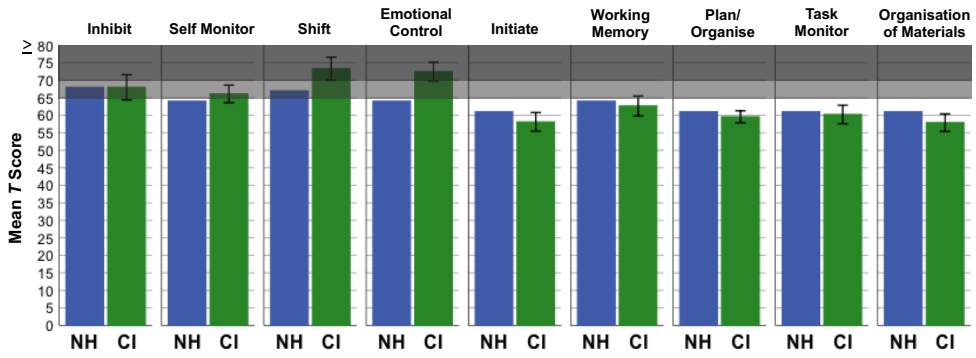


Figure 4.11: Mean *T* scores for the individual clinical scales of those NH (n = 1) and CI (n = 11) participants who had elevated GEC *T* scores on the BRIEF-2. The lightly shaded band between *T* scores of 65 and 69 represents scores between 1.5 and 2 standard deviations (SDs) above the mean *T* score distribution for the normative BRIEF-2 sample (according to the BRIEF-2 user manual) and indicate potentially clinically elevated scores. *T* scores above 70 in the darkly shaded band represent 2 SDs above the standardisation sample mean and are considered clinically elevated. Error bars represent ± 1 SEM.

potentially clinically elevated BRIEF-P scores was 22.3 months (range 10 months – 3.8 years). For the CI participants that exhibited either potentially clinically elevated or clinically elevated BRIEF-2 scores, the mean age at implantation was 21.7 months (range 12 months – 4.7 years). Since the mean age of implantation was inside the auditory sensitive period for both subgroups, and that children received their CIs as young as 10 months of age, it could be argued their clinically elevated EF scores should be considered substantial contributors to any associated less favourable language outcome.

4.4 DISCUSSION

The behavioural data presented in this chapter illustrates the substantial between-subject variability in EF performance in both NH children and paediatric CI users. With respect to NH children, as detailed throughout this discussion section, the current results align with existing literature. However, evidence relating to behavioural EF task performance in CI users of a similar age to those recruited to this thesis work is limited for comparison. In terms of performance on behavioural EF tasks, a high level of variability was observed amongst NH children of an extremely similar chronological age. This finding relates to performance on various IC and WM tasks that were administered to children aged eight months through to six years. Due to the extremely small sample size for paediatric CI users in both the cross-sectional and longitudinal studies, it was difficult to draw conclusions on performance on behavioural EF tasks

in this group of participants. However, analysis of parent-reported measures of behavioural EF in both typically-developing and deaf-implanted children revealed pronounced variability in children of extremely similar, and in some cases, the same chronological age.

In terms of behavioural performance on the A-not-B task, findings in this chapter are consistent with existing longitudinal studies that report despite NH subjects displaying individual differences in maximum delay for correct trial searches, a general linear trend in performance is observed throughout infancy and the second year with an increasing time delay required to produce task error (Cuevas & Bell, 2010; Diamond, 1985; Diamond & Goldman-Rakic, 1989; Wiebe et al., 2010).

Between-subject variability was also observed amongst NH participants on the tongue and mommy/me tasks, which were both employed to evaluate behavioural EF performance in children aged between 24 and 47 months. This is consistent with existing data from typically-developing children who performed these same tasks at a similar age to participants within this thesis (Broomell et al., 2019; Cuevas et al., 2014; Cuevas, Hubble, et al., 2012). Although floor and ceiling effects were observed for both the tongue and mommy/me tasks, persistent performance at floor level was particularly apparent for the mommy/me task. This observation is consistent with previous reports that the most challenging EF tasks for children include those that involve a combination of IC and WM,

such as the mommy/me task (Carlson, 2005). Furthermore, performance has already been reported to be more variable on the mommy/me than the tongue task in a group of typically-developing individuals performing both EF tasks (Broomell et al., 2019).

The Go/NoGo and N-back tasks were used to evaluate behavioural EF performance in children aged between 4 and 6 years of age, and consistent with data available from a similarly designed study in typically-developing children (Smith et al., 2017), a high level of between-subject variability was observed amongst NH participants for both EF tasks. Consistent with Smith et al. (2017), NH participants in this thesis had superior performance in terms of dPRIME accuracy on the N-back compared with Go/NoGo task.

Correlation analysis in this chapter revealed performance to be significantly associated with chronological age in some of the behavioural EF tasks (tongue, mommy/me, N-back), yet not others (A-not-B, Go/NoGo). This is consistent with data available from a study involving over 600 typically-developing preschool children, who were administered one or more behavioural EF task (Carlson, 2005). Twenty-four different tasks were performed in total, with chronological age of the child determining task allocation. Significant age-related improvement occurred on most tasks. The restricted age range and sample size of participants was hypothesised to account for the lack of age-related improvement in

the remaining tasks. Similarly, limited sample sizes were a potential limiting factor for all the behavioural tasks described in this thesis.

Evaluation of parent-reported measures of behavioural EF also revealed substantial between-subject variability in both NH children and paediatric CI users. This observation is consistent with existing studies performed in both preschool (Beer et al., 2014; Kronenberger et al., 2020) and school-aged children (Pisoni et al., 2008). In addition, these established studies have demonstrated CI users to score significantly worse (higher) than NH peers on the BRIEF parent-reported measure specifically. With respect to the BRIEF-2 parent-reported measure, the results in this chapter align with this evidence since CI users had significantly worse scores compared with NH participants. The current results also identified potentially clinically elevated and clinically elevated scores to be more common in paediatric CI users than NH children. The CI users described in this chapter tended to have elevated scores across all the subscales at a younger age (on the BRIEF-P), although WM and inhibit scores did appear to improve with age (on the BRIEF-2). This is consistent with existing reports that have also demonstrated preschool CI users to have significantly more problem behaviours on the BRIEF inhibit and WM clinical scales specifically (Beer et al., 2014; Kronenberger et al., 2020), and furthermore that scores in these two domains improve over time (Kronenberger et al., 2020). Paediatric CI users who had elevated scores on the BRIEF-2 in the current experiment tended to have elevated scores on the shift

subscale. Interestingly, although repeated measures of BRIEF shift scores have been shown to remain consistently lower than BRIEF inhibit and WM scores, a longitudinal study demonstrated that the shift subscale was the only BRIEF subscale to significantly predict language outcome in preschool children with CIs (Kronenberger et al., 2020).

4.5 CHAPTER SUMMARY

The current chapter examined individual variability in behavioural EF via an evaluation of performance on age-appropriate EF tasks and parent-reported measures. The findings demonstrate a substantial level of between-subject variability in individual performance on behavioural EF tasks in NH children of an extremely similar chronological age. This finding related to performance on various IC and WM tasks that were administered to children aged six months to six years of age. Most NH participants who were examined on a longitudinal basis improved their performance over time. It was difficult to draw conclusions on behavioural EF task performance in CI users due to the limited sample size of this group. However, a high level of variability in performance on parent-reported measures of EF was observed for both NH children and paediatric CI users. These findings confirm that further exploring behavioural EF, in terms of its neurodevelopmental mechanisms and its association with language outcome, in future chapters of this thesis is warranted. This chapter also highlights the importance of performing longitudinal behavioural studies, which

may not only help to establish expected and standardised trajectories of behavioural EF development but may also enable an evaluation of the impact of cochlear implantation on the rehabilitation of any identified deficiencies in EF. Unfortunately, the latter could not be examined in the current experiments due to the small sample size for CI participants.

5. THE RELATIONSHIP BETWEEN EXECUTIVE FUNCTION AND LANGUAGE PERFORMANCE

5.1 INTRODUCTION

This chapter aims to establish the association between measures of EF and language performance in both NH children and children with CIs. The first half of this chapter examines the relationship between measures of behavioural EF and language ability, not only via performance on various behavioural EF tasks, but also in terms of parent-reported measures. Unfortunately, the association between EF and language in paediatric CI users could not be analysed in the behavioural EF task-based experiments due to the small sample size associated with this group of children. However, adequate sample sizes for both NH and CI participants in the experiment that used parent-reported measures enabled the relationship between EF and language to be examined in both groups of children. The second half of this chapter presents fNIRS measurements of cortical activation to behavioural EF tasks acquired from prefrontal and superior temporal brain regions of NH and CI participants. Whilst the amplitude of activation within predefined prefrontal and superior temporal ROIs was examined in both groups, we were cautious about making any between-group comparisons due to the limited number of CI participants. Nonetheless, the sample size of the NH group allowed for the analysis of group-level cortical activation patterns and the employment of a linear mixed model (LMM) approach to determine any effect of participant age, task condition,

task performance or location of ROI on the amplitude of cortical activation detected with fNIRS. The association between cortical correlates of behavioural EF and language performance was also examined in NH participants.

5.2 BEHAVIOURAL EXECUTIVE FUNCTION AND LANGUAGE PERFORMANCE

5.2.1 Analyses

Prior to all statistical testing, descriptive statistics were used to examine assumptions of normality and homogeneity of variance. The appropriate parametric or non-parametric test was then selected accordingly based on whether the variable(s) of interest met relevant parametric assumptions. The statistical tests utilised are specified in the relevant sections throughout.

5.2.2 The Relationship Between Behavioural Executive Function Task Performance and Language Ability

5.2.2.1 Results

5.2.2.1.1 Description of the samples

To assess for any correlation between behavioural EF task performance and language ability, data for all participants (aged between 4 and 6 years) that performed the Go/NoGo and N-back tasks within three months of a language assessment was evaluated. Six NH participants within the longitudinal fNIRS experiment, in addition to the eighteen NH and two CI participants recruited to the cross-sectional fNIRS experiment were therefore included in this

analysis. As described in Chapter 3, the onset of COVID-19 halted the face-to-face PLS-5^{UK} language assessment, hence the CCC-2 parent-reported measure was used thereafter. Twelve out of the twenty-four NH participants included in the current analysis performed a PLS-5^{UK} assessment prior to the onset of the pandemic, whereas the other twelve NH subjects underwent a CCC-2 assessment. All NH participants that performed the PLS-5^{UK} completed it on the same day as the Go/NoGo and N-back tasks. The mean time between the CCC-2 assessment and the Go/NoGo and N-back tasks was 42.5 (SD 43.3) days. Both CI users underwent a PLS-5^{UK} assessment within two months of the Go/NoGo and N-back tasks. Table 5.1 summarises the participants that performed the Go/NoGo and N-back tasks according to the language assessment performed and additionally describes missing data for each of the behavioural EF tasks. As demonstrated in this table, one NH participant and one CI participant refused to perform the N-back task.

5.2.2.1.2 The Relationship Between Behavioural EF Task Performance and PLS-5^{UK} score

Performance accuracy on the Go/NoGo task (dPRIME) was not associated with PLS-5^{UK} standardised total language score (TLS) in NH participants (Pearson's correlation coefficient, *r*), r =-.24, p =.45 (2-tailed), see Figure 5.1. Furthermore, neither PLS-5^{UK} auditory comprehension (AC) or expressive communication (EC)

Table 5.1: Summary of participants performing the Go/No-Go and N-back tasks according to the language assessment performed

a) Language Assessment	b) Group	c) Mean Age in Years (SD)	d) Number of Participants	e) Missing EF Task Data	
				Go/NoGo	N-back
PLS-5^{UK}	NH (CS)		12	0	1
	NH TOTAL	5.2 (0.89)	**12**	**0**	**1**
	CI (CS)		2	0	1
	CI TOTAL	5.5 (1.6)	**2**	**0**	**1**
CCC-2	NH (CS)		6	0	0
	NH (LT)		6	0	0
	NH TOTAL	5.0 (0.71)	**12**	**0**	**0**

Column **a)** Language assessment undertaken; **b)** Experimental group in which each subject participated. CS and LT denotes participants who took part in the cross-sectional and longitudinal fNIRS experiments respectively**; c)** Mean age of each group in years (SD); **d)** Number of participants within each group; **e)** Missing behavioural data for the Go/NoGo and N-back tasks.

scores were associated with Go/NoGo performance accuracy in this cohort, r =-.35, p =.27 (AC); r =-.32, p =.31 (EC), both 2-tailed. Similar findings were observed for the N-back task, with no association between performance accuracy and PLS-5^{UK} TLS in NH subjects r =.08, p =.83 (2-tailed), see Figure 5.2. PLS-5^{UK} AC and EC scores were also not associated with N-back performance accuracy, r =-.17, p =.62 (AC); r =-.03, p =.93 (EC), both 2-tailed. Bivariate correlation analysis was not performed for CI users because only two participants performed the Go/NoGo task and only one participant performed the N-back task.

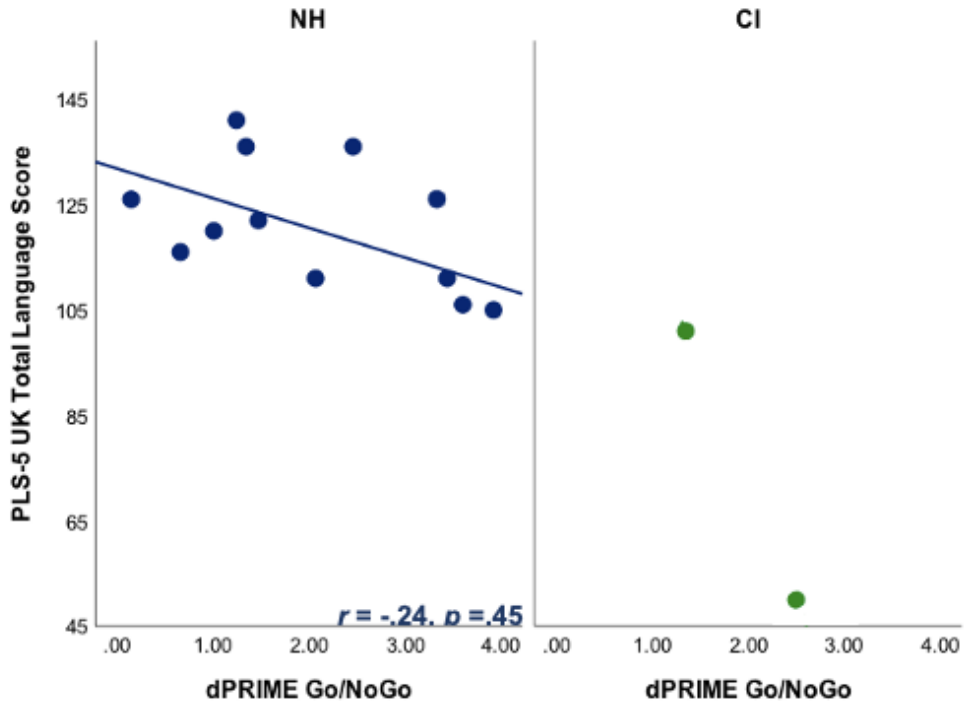


Figure 5.1: Scatterplot of performance accuracy (dPRIME) on the Go/NoGo task and PLS-5^{UK} total language score for both NH (n = 12) and CI (n = 2) participants. Regression line shown for NH participants. Increasing PLS-5^{UK} score denotes increasing language proficiency and increasing dPRIME reflects superior task performance.

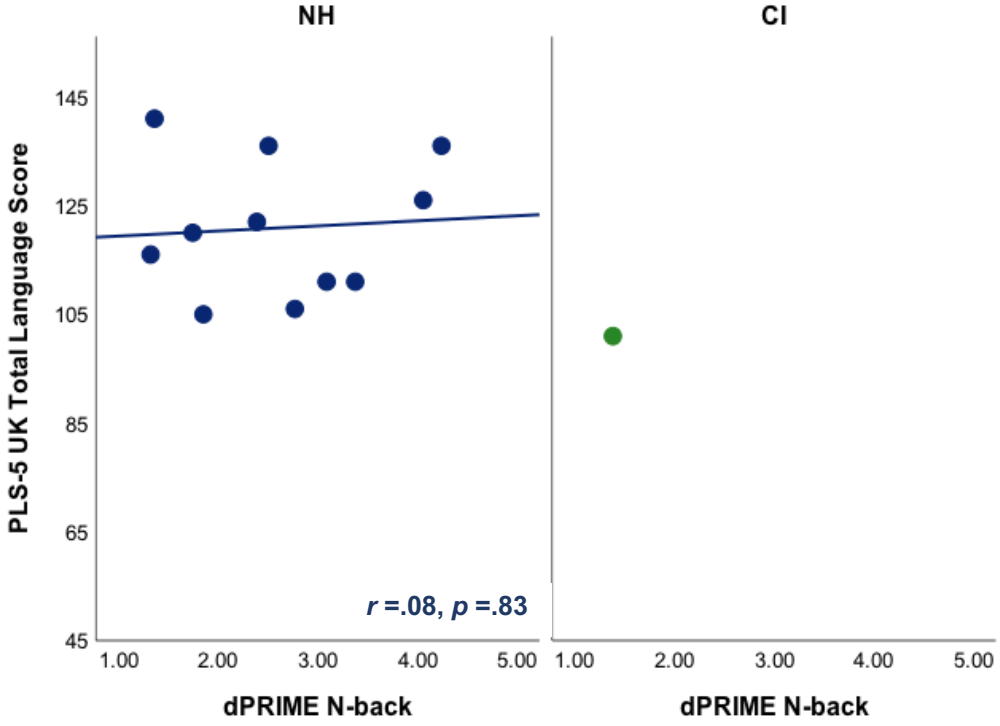


Figure 5.2: Scatterplot of performance accuracy (dPRIME) on the N-back task and PLS-5^{UK} total language score for NH (n = 11) and CI (n = 1) participants. Regression line is shown for NH participants. Increasing PLS-5UK score denotes increasing language proficiency and increasing dPRIME reflects superior task performance.

5.2.2.1.3 The Relationship Between Behavioural EF Task Performance and CCC-2 score

With respect to the relationship between performance on the Go/NoGo task and parent-reported measures of communication and language, no significant association was observed between task accuracy (dPRIME) and standardised CCC-2 General Communication Composite (GCC) score in NH participants (Kendall's tau-b correlation coefficient), T_b =.22, p =.34 (2-tailed), see Figure 5.3. Similarly, no significant association was observed between N-back accuracy and CCC-2 performance, T_b =.11, p =.63 (2-tailed), see Figure 5.4. Once again, bivariate correlation analysis was not performed for CI users due to the limited sample size.

During the COVID 19 pandemic, it was decided that language assessments within the longitudinal experiment would be timed for 12 months after the date of the first research session for NH participants, and 12 months after device activation for CI users. This meant that despite face-to-face testing sessions eventually recommencing, language assessments did not always coincide with the final testing session for longitudinal participants (since many parent/guardians had already completed a parent-reported measure of language ability prior to attending a final face-to-face testing session). Hence, the correlation between language ability and performance on each of the A-not-B, tongue and mommy/me tasks (that were only undertaken as part of the longitudinal experiment) unfortunately could not be examined due to restricted sample sizes.

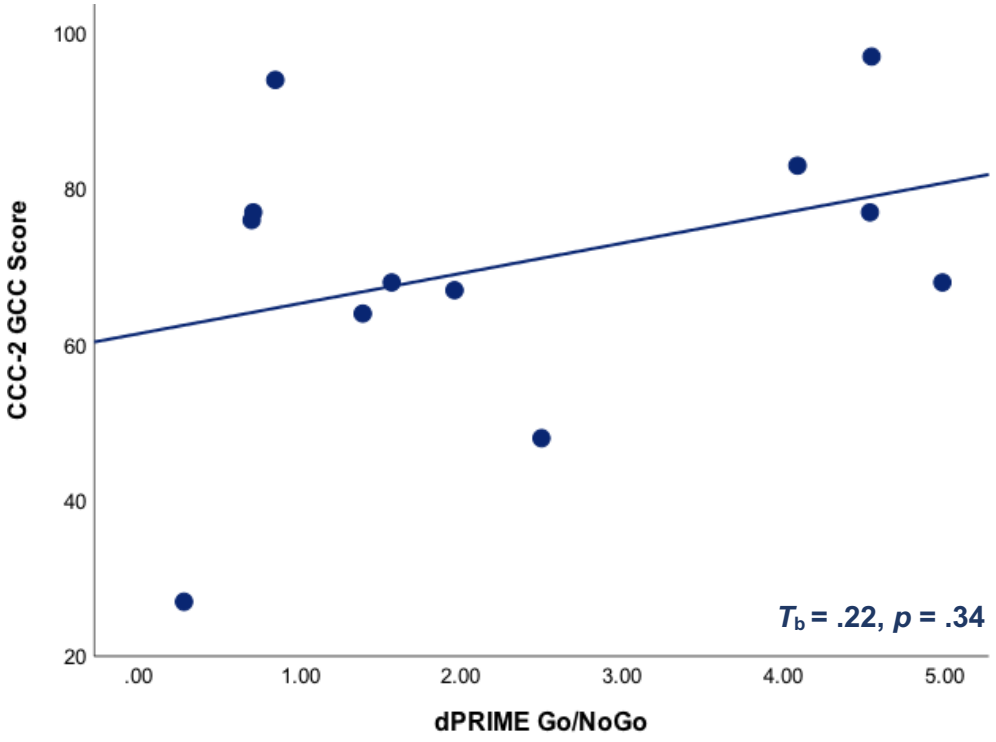


Figure 5.3: Scatterplot of performance accuracy (dPRIME) on the Go/NoGo task and CCC-2 General Communication Composite (GCC) score for NH (n = 12) participants with regression line shown. Increasing CCC-2 GCC score denotes increasing communication and language proficiency.

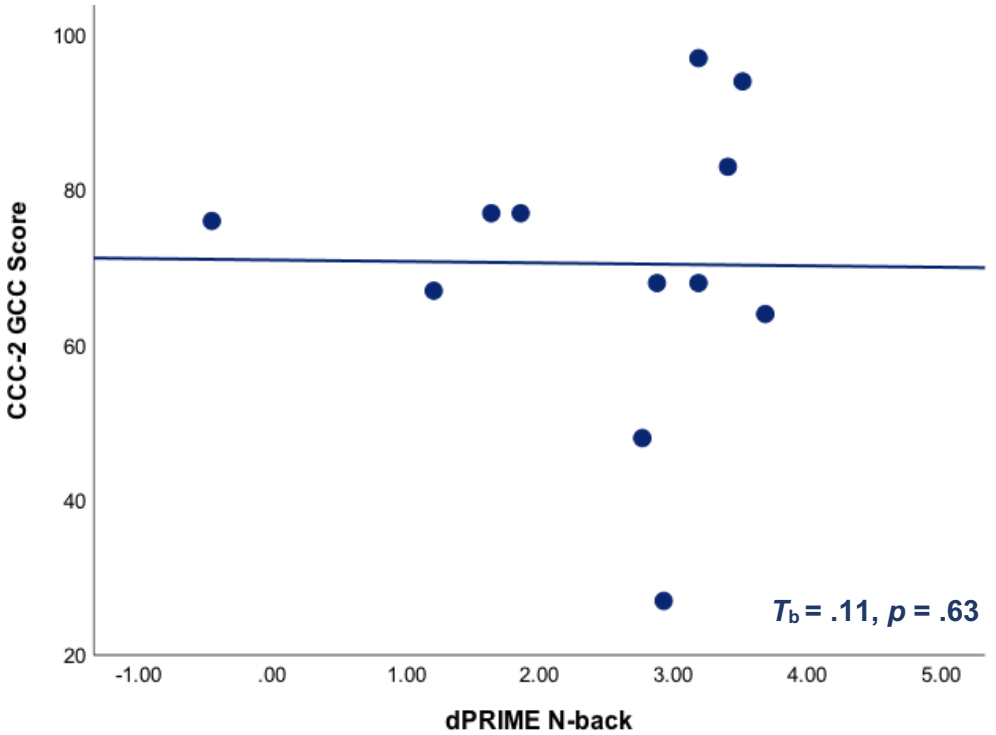


Figure 5.4: Scatterplot of performance accuracy (dPRIME) on the N-back task and CCC-2 General Communication Composite (GCC) score for NH (n = 12) participants with regression line shown. Increasing CCC-2 GCC score denotes increasing communication and language proficiency.

5.2.3 The Relationship Between Parent-Reported Measures of Behavioural Executive Function and Language Performance

5.2.3.1 Results

5.2.3.1.1 Description of the samples

Participants for whom both the Behaviour Rating Inventory of Executive Function (BRIEF) and CCC-2 parent-reported measures were completed were included in this analysis. All participants were aged between 4 and 6 years. In all cases, the BRIEF and CCC-2 assessment forms were completed on the same day. Table 5.2 summarises these participants according to NH and CI groups, in addition to the experiment in which they each participated. In Chapter 4 of this thesis, performance on the BRIEF parent-reported measure was described according to the version of the assessment that was completed i.e. BRIEF-P or BRIEF-2. The purpose of this was to identify participants with clinically elevated scores, which are available only for the BRIEF-2 version, hence these scores wouldn't apply to participants undertaking BRIEF-P. In this current chapter, BRIEF performance data is presented without specification of the version completed. The amalgamation of BRIEF data is a common technique amongst studies that have used multiple versions of the BRIEF tool (Kronenberger et al., 2020; Pisoni et al., 2010) and is statistically catered for by the ability to convert raw scores to *T* scores (using age-based normative samples) in both the BRIEF-P and BRIEF-2 version.

Table 5.2: Summary of participants for whom parent-reported measures of EF (BRIEF) and language (CCC-2) were completed

Group	Number of Participants	Mean Age in Years (SD)
NH (LT)	9	
NH (CS)	6	
NH (PRM)	41	
NH TOTAL	**56**	**5.2 (0.83)**
CI (LT)	1	
CI (CS)	0	
CI (PRM)	41	
CI TOTAL	**42**	**5.4 (0.94)**

LT, CS and PRM denote participants recruited to the longitudinal, cross-sectional and parent-reported measures experiment respectively. SD = Standard deviation.

5.2.3.1.2 The Association Between Parent-Reported Measures of Executive Function (BRIEF) and Language (CCC-2)

The association between parent-reported measures of EF and language performance was examined via the use of BRIEF GEC *T* scores and standardised CCC-2 GCC scores. In terms of the CCC-2 assessment, consistent with existing reports (A. E. Geers et al., 2003; A. Jones et al., 2020; Kronenberger et al., 2020), children with CIs tended to have lower communication and language performance than NH peers, see Figure 5.5. An independent *t*-test revealed a significant difference in the CCC-2 GCC score for NH participants (mean = 79.6, SD 16.9) compared with CI users (mean = 59.0, SD 20.9), $t(96) = 5.40$, $p<.001$ (2-tailed). With respect to parent-reported measures of EF, an independent *t*-test revealed CI users to have significantly higher BRIEF GEC *T* scores (mean = 56.81, SD 12.8) compared with NH participants (mean = 49.4, SD

8.1), $t(65) = 3.28$, $p<.01$ (2-tailed), see Figure 5.6. The observation of less favourable BRIEF scores amongst CI users has previously been addressed in Chapter 4 of this thesis.

Bivariate correlation analysis revealed a significant association between BRIEF GEC and CCC-2 GCC scores in both NH ($r = -.512$, $p<.001$, 2-tailed) and CI ($r = -.731$, $p<.001$, 2-tailed) participants, see Figure 5.7. Interestingly, a significant difference in the Pearson correlation coefficients for the NH and CI groups was observed, signifying that parent-reported measures of EF and language more strongly correlated in paediatric CI users than NH children (z test statistic = -1.73, $p<.05$ [1]). For reasons described in Chapter 3, the elements of IC and WM are specifically focused upon in this thesis when examining EF. Therefore, bivariate correlation analysis was also performed to evaluate the relationship between the CCC-2 GCC score and the *T* score for each of the individual 'inhibit' and 'working

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[1] The z test statistic was calculated by firstly transforming the correlation coefficient, or r value for each participant group, into a z score (Fisher's r to z transformation). The observed z test statistic was then calculated using the formula:

$z_{observed} = (z_1 - z_2) / (\text{square root of } [1/N_1 - 3) + (1/N_2 - 3)]$

Where z_1 and z_2 correspond to the correlation coefficients (r), and N_1 and N_2 denote the sample size, of each participant group.

memory (WM)' scales available in both versions of the BRIEF assessment tool. In NH participants, the CCC-2 GCC score was significantly associated with the inhibit scale *T* score (T_b =-.27, p<.01, 2-tailed), whereas there was no association between CCC-2 GCC score and the WM scale *T* score (see Figure 5.8). Interestingly, in CI participants the CCC-2 GCC score was significantly associated with the *T* score for both the inhibit and WM scales, r = -.602, p<.001 (inhibit); T_b =-.53, p<.001 (WM), both 2-tailed (see Figure 5.9).

The current results demonstrate that parent-reported measures of behavioural EF and language are significantly correlated in both NH and deaf-implanted children, whereas there is no significant association between performance on the Go/NoGo and N-back behavioural EF tasks and language ability in NH participants. Therefore, bivariate correlation analysis was performed to assess the association between performance on each of these behavioural EF tasks (dPRIME) and parent-reported measures of EF (BRIEF *T* scores) in the group of NH children. Interestingly, there was no association between performance on Go/NoGo (dPRIME) and BRIEF (GEC *T* score), T_b =.27, p =.44, 2-tailed (n = 24). Furthermore, there was no significant correlation between N-back performance (dPRIME) and BRIEF (GEC *T* score) T_b =.35, p =.26, 2-tailed (n = 23).

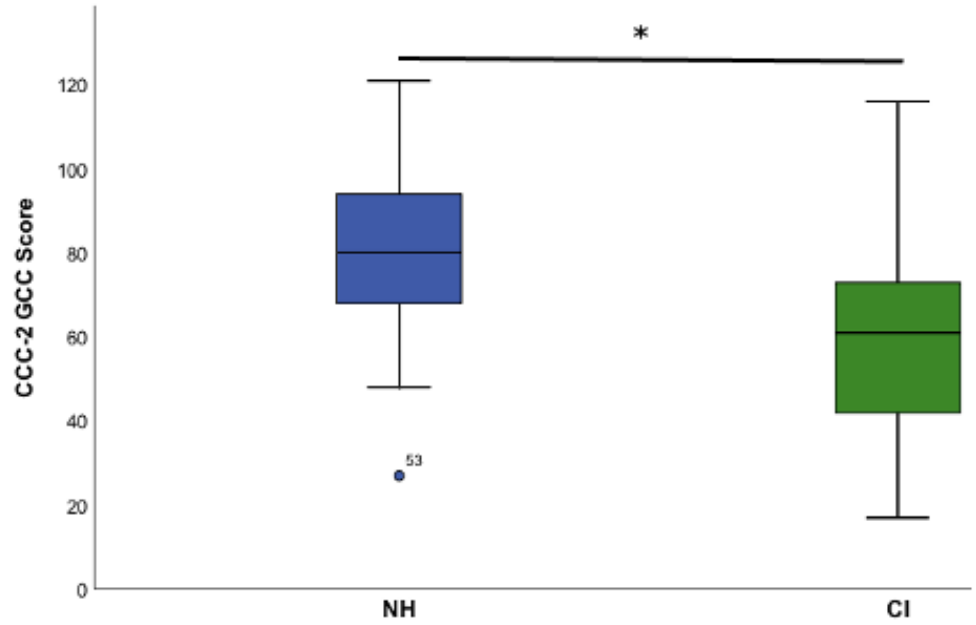


Figure 5.5: Boxplot displaying performance on the CCC-2 parent-reported measure of language for NH (n = 56) participants and CI users (n = 42).
*p <.001, 2-tailed.

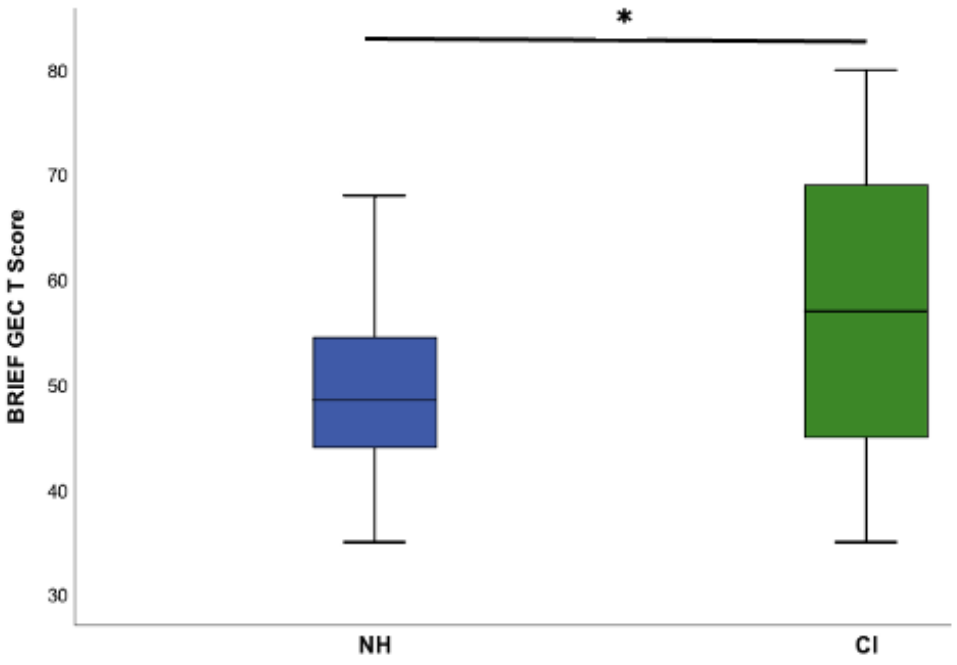


Figure 5.6: Boxplot displaying performance on the BRIEF parent-reported measure of executive function for NH (n = 56) participants and CI users (n = 42).
**p* <.01, 2-tailed.

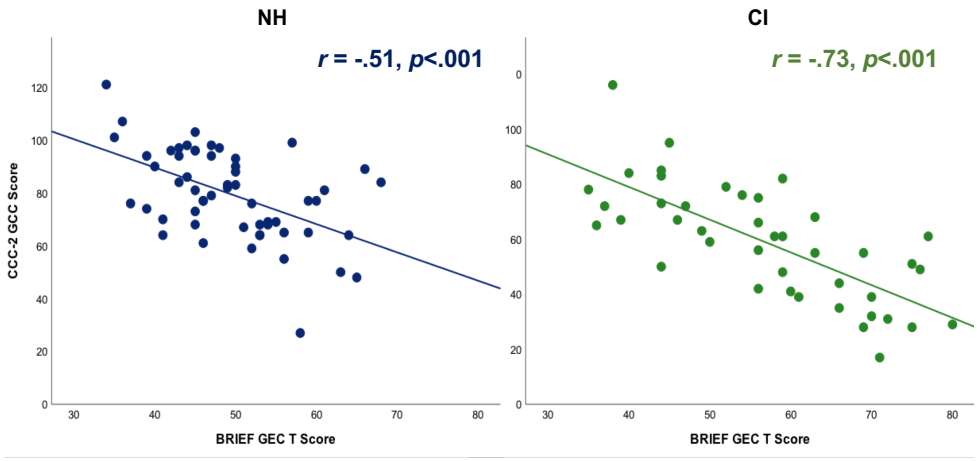


Figure 5.7: Scatterplot of performance on BRIEF and CCC-2 parent-reported measures for NH (n = 56) and CI (n = 42) participants with best fitting linear regression lines shown. Increasing CCC-2 GCC score denotes increasing communication and language proficiency, whilst increasing BRIEF GEC *T* Score represents less favourable executive function.

5.3 CORTICAL CORRELATES OF BEHAVIOURAL EXECUTIVE FUNCTION AND THEIR RELATIONSHIP WITH LANGUAGE PERFORMANCE

5.3.1 Analyses

To examine cortical responses during the behavioural Go/NoGo and N-back tasks, beta weights representing the amplitude of cortical activation for each condition within each task were extracted for each measurement channel across the optode array (see section 3.5.2 for details) and were subjected to the statistical testing described below.

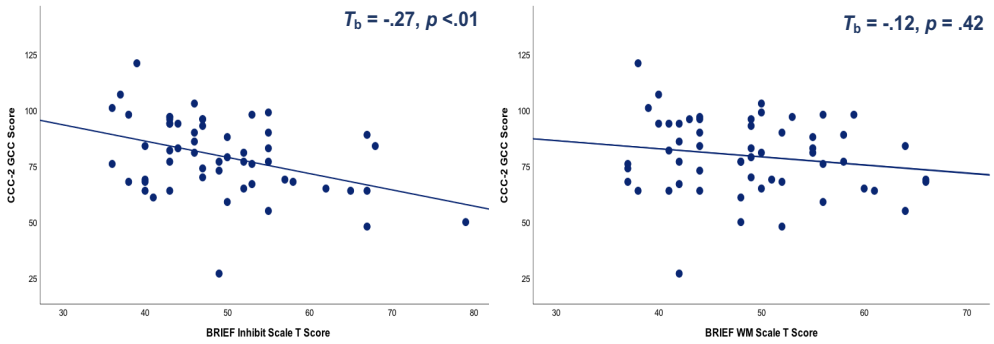


Figure 5.8: Scatterplots of performance on BRIEF 'inhibit' and 'working memory (WM)' scales and CCC-2 parent-reported measures for NH participants (n = 56) with best fitting linear regression lines shown. Increasing CCC-2 GCC score denotes increasing communication and language proficiency, whilst increasing BRIEF *T* score represents less favourable performance on the inhibit and WM scales.

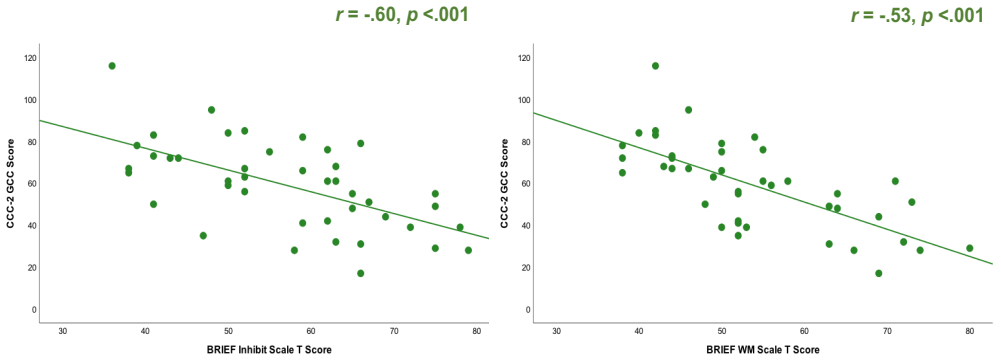


Figure 5.9: Scatterplots of performance on BRIEF 'inhibit' and 'working memory (WM)' scales and CCC-2 parent-reported measures for CI participants (n = 42) with best fitting linear regression lines shown. Increasing CCC-2 GCC score denotes increasing communication and language proficiency, whilst increasing BRIEF *T* score represents less favourable performance on the inhibit and WM scales.

5.3.1.1 Cortical Activation Maps

For each condition within the Go/NoGo and N-back tasks, group-level cortical activation maps were produced to visualise patterns of behavioural EF task-evoked cortical activation across the fNIRS measurement arrays for the NH participants. Unfortunately, it was not possible to produce cortical activation maps for the CI participants due to the associated sample size. For each condition within a task (i.e. the Go and NoGo conditions within the Go/NoGo task and the 0-back and 1-back conditions within the N-back task), single sample, one-tailed *t*-tests were conducted on the beta weights to detect measurement channels that displayed significant levels of cortical activation compared to rest. The same statistical analysis was also performed to detect which measurement channels detected significantly increased cortical activation from the control to the EF condition (i.e. from the Go to the NoGo condition and from the 0-back to the 1-back condition). However, by testing for significant activation in all 52 individual measurement channels, multiple comparisons are performed and the risk of Type I error is increased. These multiple comparisons were accounted for by applying the false discovery rate (FDR method) across channels (Benjamnini & Hochberg 1995). The original formulation of the FDR procedure, which assumes independence or slight positive dependency across tests, was used in line with recommendations for fNIRS data analysis (Singh & Dan, 2006). Statistical significance was assessed against an FDR-corrected threshold of $q < .05$.

5.3.1.2 Region of Interest Analysis

For each condition within the Go/NoGo and N-back tasks, the time course of cortical activation within the predefined ROIs (see section 3.5.4 for details) was plotted. This enabled visualisation of the behavioural EF-evoked haemodynamic responses to determine whether plausible, artefact-free, HRFs had been obtained in each task condition. For each measurement channel, the time course of HbO and HbR concentration changes were block-averaged using the HOMER2 hmrBlockAvg function (Huppert et al., 2009). For each task condition these were then averaged over the relevant measurement channels to produce separate time courses for each ROI.

Following the use of a GLM approach (see section 3.5.2), the resultant beta weights representing the amplitude of cortical activation were averaged across the ROI measurement channels for each participant. To investigate cortical responses to the Go/NoGo and N-back tasks in NH participants, beta weights for each condition were subjected to statistical testing using a LMM. A LMM is a parametric linear model that enables the relationship between a continuous dependent variable and various predictor variables within repeated-measures datasets to be analysed (West et al., 2007). Unfortunately, the sample size for CI users prevented statistical analysis with LMMs for this group. However, to investigate EF-evoked cortical activation in NH participants during both the Go/NoGo and N-back tasks, beta weights were analysed separately

for each ROI. Two LMMs were performed for each ROI. The first LMM included two fixed factors of 'condition' and 'age group' to estimate the fixed effect of task condition and age on behavioural EF-evoked cortical activation within each ROI. In addition, a 'condition – age group' interaction term was specified to understand whether an effect of condition on cortical activation differed between younger and older children. Age was represented as a continuous variable, but a median split of 4.9 years was used to allocate participants to either a 'younger' or 'older' age group so that the effect of age could be evaluated as a categorical variable within the model. To evaluate the effect of task performance (in terms of dPRIME accuracy) on behavioural EF-evoked cortical activation, the covariate 'performance (dPRIME)' was entered into the second LMM as a fixed effect. To account for variance related to age, 'age' was also specified as a fixed covariate in this LMM. In all LMMs, a random intercept for 'participant' was included with 'scaled identity' selected as the covariance type to account for the correlation between beta weights within a participant. A restricted maximum likelihood estimation method was adopted for all LMMs.

5.3.2 Results

5.3.2.1 Description of the Samples

The twenty-four NH and two CI participants described in Table 5.1 were initially selected for this analysis. As previously described in section 5.2.2, one NH participant (NH (CS)_01) and one CI participant (CI (CS)_01) refused to perform the N-back task.

Furthermore, participant NH (CS)_01 refused to wear the fNIRS equipment whilst performing the Go/NoGo task. Visual examination of the data revealed that the analysis procedure failed to produce valid numerical values for the chromophore concentration changes in a small number of cases, typically because of poor quality in the raw fNIRS signals. Channels suffering from this issue were excluded from further analysis. A number of these 'bad channels' were evident across three NH participants, the details of which are provided in Table 5.3. Seven channels had to be excluded for participant CI (CS)_01, many of which formed part of the predefined EF and auditory ROIs, hence data for this participant were excluded from the analysis. Following a review of the researcher's testing notes, it was assumed that the 'bad channels' for all participants were due to poor optode-scalp coupling and the attenuation of light by dark hair. Following the exclusion of participant CI (CS)_01, fNIRS cortical activation data acquired from twenty-three NH participants and one CI participant during the Go/NoGo and N-back tasks was subjected to analysis. Table 5.3 summarises the reasons behind missing data for the Go/NoGo and N-back tasks according to each individual participant.

5.3.2.2 Model Diagnostics

For each LMM analysis conducted, the model's residuals were assessed by examining histograms, Q-Q plots, as well as the

Table 5.3: Summary of missing fNIRS data and excluded fNIRS measurement channels

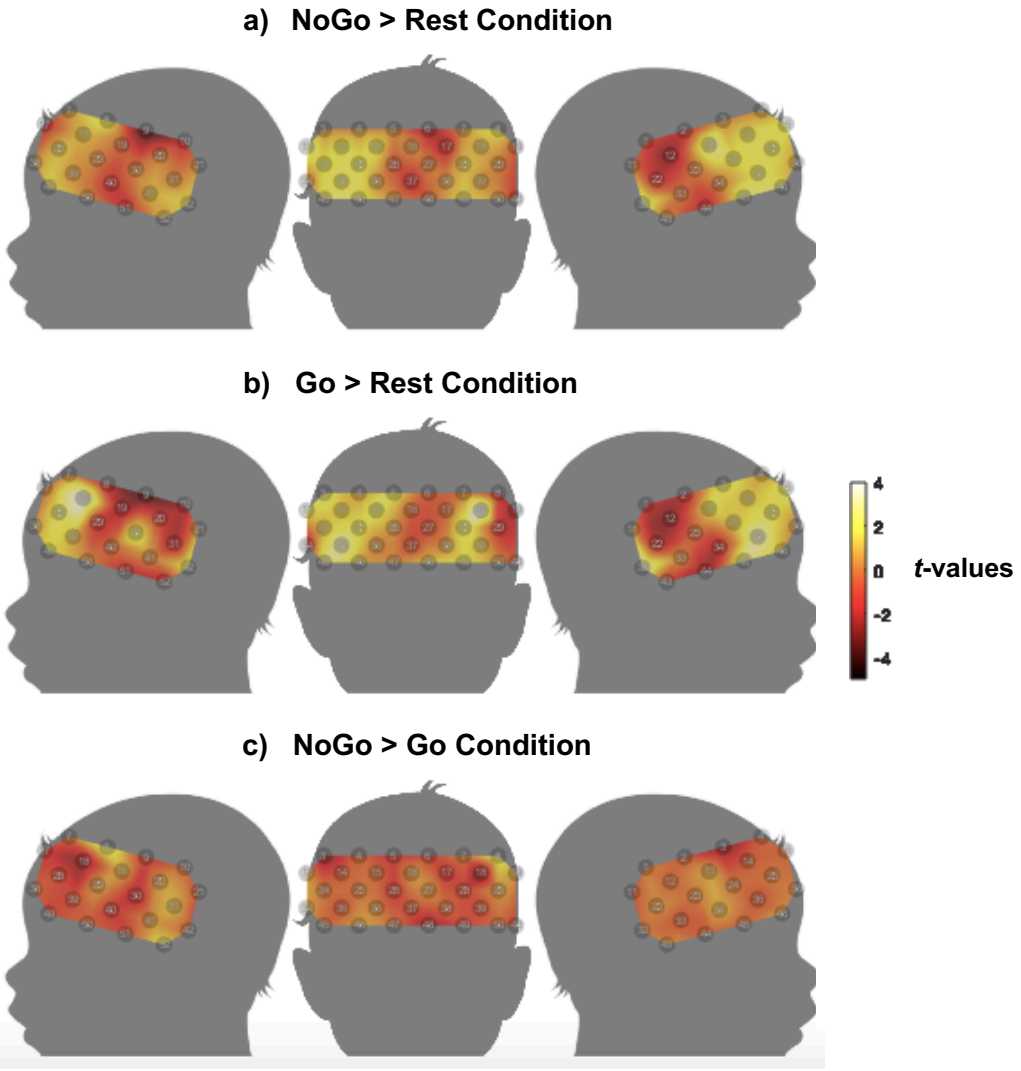
Participant ID	Missing fNIRS Data	Excluded fNIRS Measurement Channels
NH (CS)_01	Participant refused to wear fNIRS equipment, hence no Go/NoGo or N-back fNIRS data	-
NH (CS)_03	-	#3,8
NH (CS)_09	-	#10
NH (CS)_13	-	#5,10
CI (CS)_01	Participant excluded from analysis due to several 'bad' fNIRS channels within the predefined EF and auditory ROIs	#8,10, 26, 27, 36, 38, 41

The number of participants with missing fNIRS data for the behavioural Go/NoGo and N-back tasks is demonstrated. The excluded fNIRS measurement channels or 'bad channels' are also summarised. These channels were excluded due to the absence of valid numerical values in the fNIRS raw chromophore concentration data.

Shapiro Wilk test. These examinations suggested that the residuals of the LMMs conducted for both auditory ROIs and the newly defined channel #8 ROI (see next section 5.3.2.3 for details) in the Go/NoGo task, and the left BA 10 and left BA 46 ROIs in the N-back task, appeared to be driven by skew. Hence this violation of normality may have affected the accuracy with which the LMMs estimated parameters within each of these ROIs. The residuals for the LMMs conducted for the other ROIs in the Go/NoGo and N-back tasks were approximately normally distributed.

5.3.2.3 Cortical Activation to Go/NoGo Behavioural Executive Function Task

Figure 5.10 displays group-level cortical activation maps for NH participants for the Go/NoGo task. One tailed t-tests (q<.05, FDR corrected) revealed that no measurement channels were significantly activated across the group of NH participants in either task condition compared with rest. However, despite not reaching statistical significance, increased cortical activation was observed in at least one channel within each of the predefined bilateral EF and auditory ROIs during the NoGo response inhibition condition (see Figure 5.10a). A similar pattern of cortical activation was seen for the Go control condition (see Figure 5.10b). Increased cortical activation from the Go to the NoGo condition was apparent in the predefined left auditory ROI overlying the left superior temporal cortex and in left-sided channel #8 (see Figure 5.10c). Although channel #8 was not included in any of the predefined EF ROIs, the utilisation of mean head size measurements for participants included in this analysis combined with the international 10-20 system (as outlined in section 3.5.4), suggested that channel #8 overlayed left BA 46. Although the predefined 'left BA 46' ROI was also estimated to cover this region of the lateral PFC, channel #8 was measured to overlay BA 46 within a more posterior and dorsal area of the left lateral PFC. Throughout this chapter and for the Go/NoGo task specifically, channel #8 is considered a separate EF ROI to the 'left BA 46' ROI with the aim of analysing cortical activation detected by this channel specifically.



ROI Name	Channels
Right BA 10	#26,36,47
Left BA 10	#27,38,48
Right BA 46	#25,35,46
Left BA 46	#28,39,49
Right Auditory	#32,33,43
Left Auditory	#41,42,52
Channel 8	#8

Figure 5.10: Group-level cortical activation maps for NH participants during the Go/NoGo task. **a)** NoGo condition > rest condition; **b)** Go condition > rest condition; **c)** NoGo > Go condition. Amplitude of cortical activation is colour coded by *t*-value. Although no significantly activated channels were identified, they were examined for with one-tailed *t*-tests (q <.05, FDR corrected). **n = 23.** Note the maps are interpolated from single-channel results and the overlay onto a paediatric template is for illustrative purposes only.

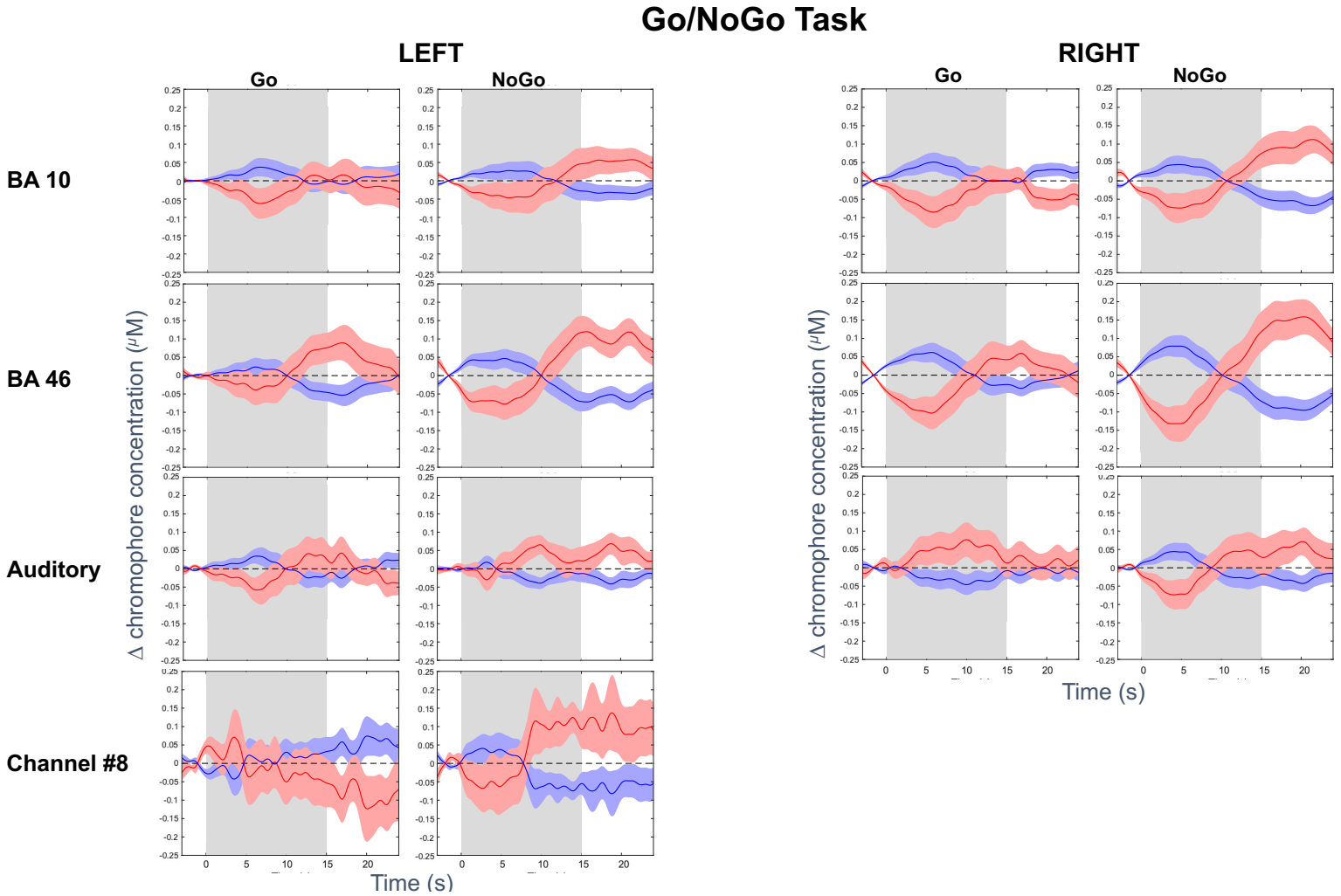
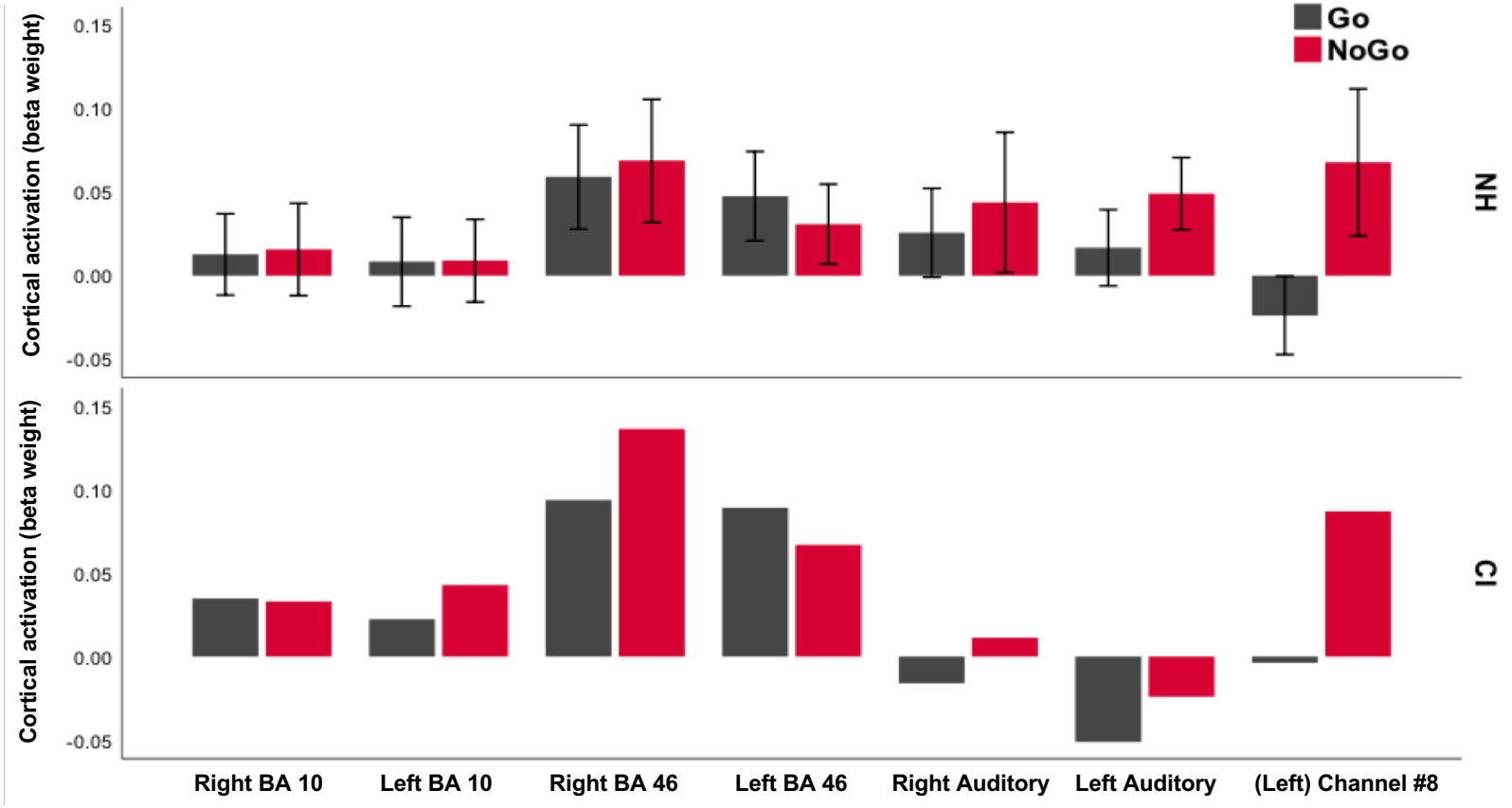


Figure 5.11: Group-averaged time courses of activation to the Go/NoGo task for NH participants. Changes in HbO and HbR concentration are shown for both the Go and NoGo condition of the task (compared with rest) in each of the defined ROIs. LEFT and RIGHT relate to the hemisphere in which each ROI is located. Stimulation period indicated by shaded grey region. Coloured shading indicates ± 1 standard error of the mean across participants. **n = 23.**

Figure 5.11 shows the group-averaged time course of activation within the EF and auditory ROIs for each condition within the NH group. These plots indicate that plausible HRFs elicited by the Go and NoGo conditions were acquired from NH participants, whereby an increase in HbO with a simultaneous decrease in HbR concentration was observed in many of the ROIs, reflecting the canonical HRF. This canonical response was particularly apparent in the channel #8 ROI during the NoGo condition. Due to the limited sample size, responses from the CI group are not illustrated here but visual inspection of the raw data showed that these responses were free from any device related artefacts.

Figure 5.12 shows the mean beta weight derived from each ROI during the Go and NoGo conditions for NH participants, in addition to beta weights for the one CI participant. With respect to the NH group, substantial between-subject variability was observed for the amplitude of task-induced cortical activation, a finding apparent for both conditions across all ROIs. Increased activation during the NoGo condition was particularly apparent in channel #8, bilateral auditory and right BA 46 ROIs. Consistent with the cortical activation maps, increased activation was observed during the Go condition across most ROIs, albeit predominantly in bilateral BA 46 ROIs. Furthermore, the beta weight increased substantially from the Go to the NoGo condition in channel #8 and the left auditory ROI. Although extreme caution should be exercised when making comparisons, akin to NH participants, cortical activation increased

Figure 5.12: Bar chart showing mean amplitude of cortical activation during the Go/NoGo task for NH participants and one CI user



This bar chart shows beta weights for the NH participants (mean for n = 23 participants) and one CI user. Error bars show ±1 standard error of the mean (SEM).

Table 5.4: Summary of Linear Mixed Model (LMM) analysis by Region of Interest (ROI) for NH participants performing the Go/NoGo task

a) ROI	b) Condition	c) Age group	d) Condition*Age group	e) Task performance
Right BA 10	No significant main effect ($F_{1,21}$=.00, p= .99)	No significant main effect ($F_{1,21}$ =.01, p=.93)	Significant interaction between condition and age group ($F_{1,21}$ = 6.44, p<.05), with children in the older age group displaying significantly greater cortical activation during the NoGo compared with the Go condition (mean difference in beta weight = 0.064)	No significant main effect during Go ($F_{1,20}$ =.39, p=.53) or NoGo condition ($F_{1,20}$ =.05, p=.83)
Left BA 10	No significant main effect ($F_{1,21}$=.00, p=.99)	No significant main effect ($F_{1,21}$ =.08, p=.78)	No significant interaction ($F_{1,21}$ =.56, p=.46)	No significant main effect during Go ($F_{1,20}$ =.37, p=.55) or NoGo condition ($F_{1,20}$ =.11, p=.74)
Right BA 46	No significant main effect ($F_{1,21}$=.07, p=.79)	No significant main effect ($F_{1,21}$ =.14, p=.71)	No significant interaction ($F_{1,21}$ =1.31, p=.27)	No significant main effect during Go ($F_{1,20}$ =1.32, p=.26) or NoGo condition ($F_{1,20}$ =.22, p=.88)
Left BA 46	No significant main effect ($F_{1,21}$=.26, p=.61)	No significant main effect ($F_{1,21}$ =.04, p=.84)	No significant interaction ($F_{1,21}$ =.18, p=.68)	No significant main effect during Go ($F_{1,20}$ =.77, p=.39) or NoGo condition ($F_{1,20}$ =.48, p=.49)
Right Auditory	No significant main effect ($F_{1,21}$=.11, p=.75)	No significant main effect ($F_{1,21}$ =.13, p=.72)	No significant interaction ($F_{1,21}$ =.88, p=.36)	No significant main effect during Go ($F_{1,20}$ =.32, p=.58) or NoGo condition ($F_{1,20}$ =.61, p=.44)
Left Auditory	No significant main effect ($F_{1,21}$=1.56, p=.22)	No significant main effect ($F_{1,21}$ =2.23, p=.15)	After adjusting for main effects, children in the older age group displayed greater cortical activation with increasing age during the NoGo compared with the Go condition (β =0.095, SE =.03, t=3.21, p<.05)	No significant main effect during Go ($F_{1,20}$ =.04, p=.84) or NoGo condition ($F_{1,20}$ =2.90, p=.10)
(Left) Channel #8	Significant main effect of condition ($F_{1,21}$=5.23, p<.05), with greater cortical activation observed during the NoGo compared with the Go condition (mean difference in beta weight = 0.099)	No significant main effect ($F_{1,21}$ =4.38, p=.051)	Significant interaction between condition and age group ($F_{1,21}$ = 3.84, p<.05), with children in the younger age group displaying significantly greater cortical activation during the NoGo compared with the Go condition (mean difference in beta weight = 0.177)	No significant main effect during Go ($F_{1,20}$ =.94, p=.34) or NoGo ($F_{1,20}$ =.09, p=.77)

Summary of LMM analysis performed for the Go/NoGo task for each ROI shown in column **a)**. Column **b)** details any main effect of condition on beta weight; column **c)** describes any main effect of age group on beta weight; column **d)** details any interaction between condition and age group on beta weight and; column **e)** describes any main effect of task performance (dPRIME) on the beta weight during the Go condition and NoGo condition after accounting for variance relating to age. Significant findings are highlighted in red (p<.05).

substantially from the Go to the NoGo condition in channel #8 for the CI user. Conversely however, a relative deactivation compared to rest was seen in the left auditory ROI of the CI participant during both the Go and NoGo conditions. LMM analysis of beta weights within each ROI for NH participants performing the NoGo task is summarised in Table 5.4. Statistically significant findings included a significant interaction between condition and age group ($F_{1,21}$ = 6.44, p <.05) in the right BA 10 ROI, with older children ($\geq$4.9 years) displaying a significantly higher amplitude of cortical activation in the NoGo condition compared with Go condition (mean difference in beta weight = 0.064). After adjusting for main effects, there was a significant interaction between condition and age group in the left auditory ROI, with older children displaying greater cortical activation with increasing age during the NoGo condition compared with the Go condition (β = 0.095, SE = .03, t = 3.21, p<.05). In the left-sided channel #8 ROI, there was a significant main effect of condition ($F_{1,21}$ = 5.23, p<.05) with a greater amplitude of cortical activation during the NoGo compared with the Go condition (mean difference 0.099). This effect appears to have been driven by age, as a significant interaction between condition and age group ($F_{1,21}$ = 3.84, p<.05) was also observed, with younger children (<4.9 years) displaying significantly increased cortical activation during the NoGo compared with Go condition (mean difference in beta weight 0.177).

5.3.2.4 Cortical Activation to N-back Behavioural Executive Function Task

Figure 5.13 displays the group-level cortical activation maps for NH participants for the N-back task according to condition. One tailed t-tests (q<.05, FDR corrected) revealed no measurement channels to be significantly activated across the group of NH participants in either condition. Despite not reaching statistical significance, increased cortical activation was observed within all predefined EF ROIs and the left auditory ROI during the 1-back condition, see Figure 5.13a. During the 0-back condition, increased cortical activation was observed in all predefined EF and auditory ROIs, with substantial activation noted in the right BA 46 ROI, see Figure 5.13b. Increased activation from the 0-back to the 1-back condition was apparent in the left BA 46 ROI and in channel #40 within the left hemisphere. The utilisation of participant head size measurements and the international 10-20 system suggested channel #40 overlaid BA 44 within the left VLPC. Throughout this chapter, channel #40 is therefore considered an individual EF ROI for the N-back task specifically.

Figure 5.14 shows the group-averaged time course of activation within the EF and auditory ROIs for each condition during the N-back task for NH participants. These plots indicate that plausible HRFs elicited by the 0-back and 1-back conditions were acquired from NH participants. An increase in HbO with a simultaneous decrease in HbR concentration was particularly apparent in the left-sided channel #40 during the 1-back condition. Interestingly

ROI Name	Channels
Right BA 10	#26,36,47
Left BA 10	#27,38,48
Right BA 46	#25,35,46
Left BA 46	#28,39,49
Right Auditory	#32,33,43
Left Auditory	#41,42,52
Channel 40	#40

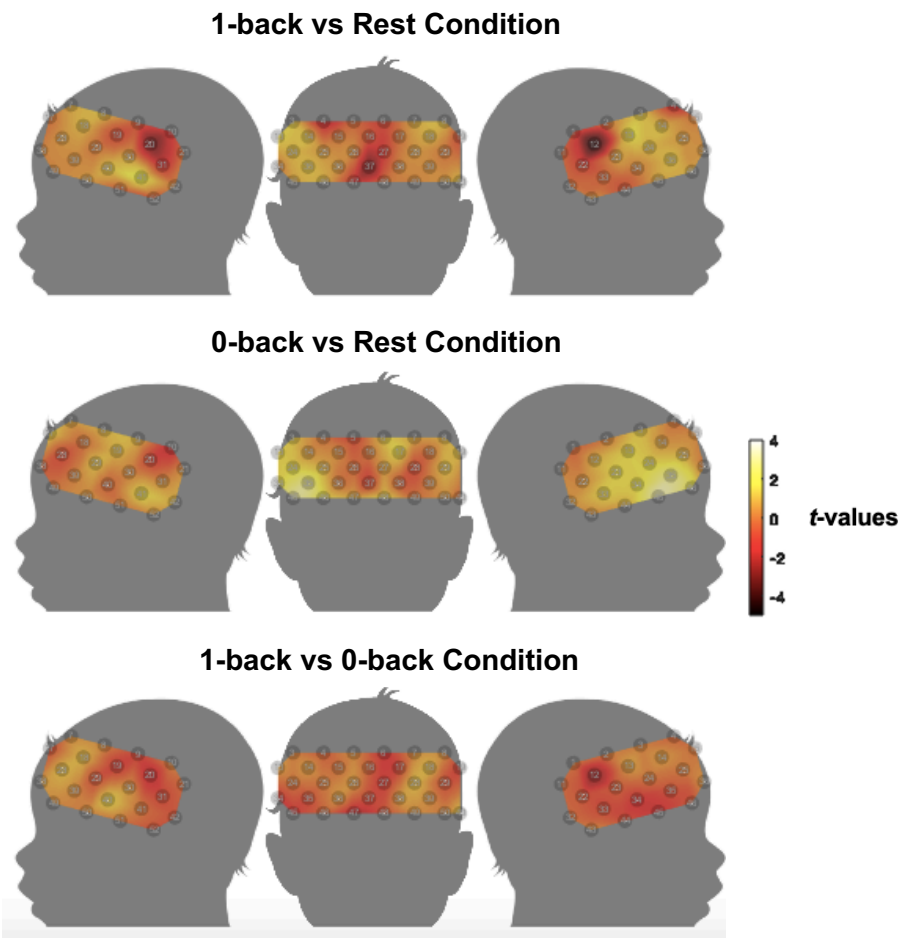


Figure 5.13: Group-level cortical activation maps for NH participants during the N-back task. **a)** 1-back condition > rest condition; **b)** 0-back condition > rest condition; **c)** 1-back > 0-back condition. Amplitude of cortical activation is colour coded by *t*-value. Although no significantly activated channels were identified, they were examined for with one-tailed *t*-tests (q <.05, FDR corrected). **n = 23.** Note the maps are interpolated from single-channel results and the overlay onto the paediatric template is for illustrative purposes only.

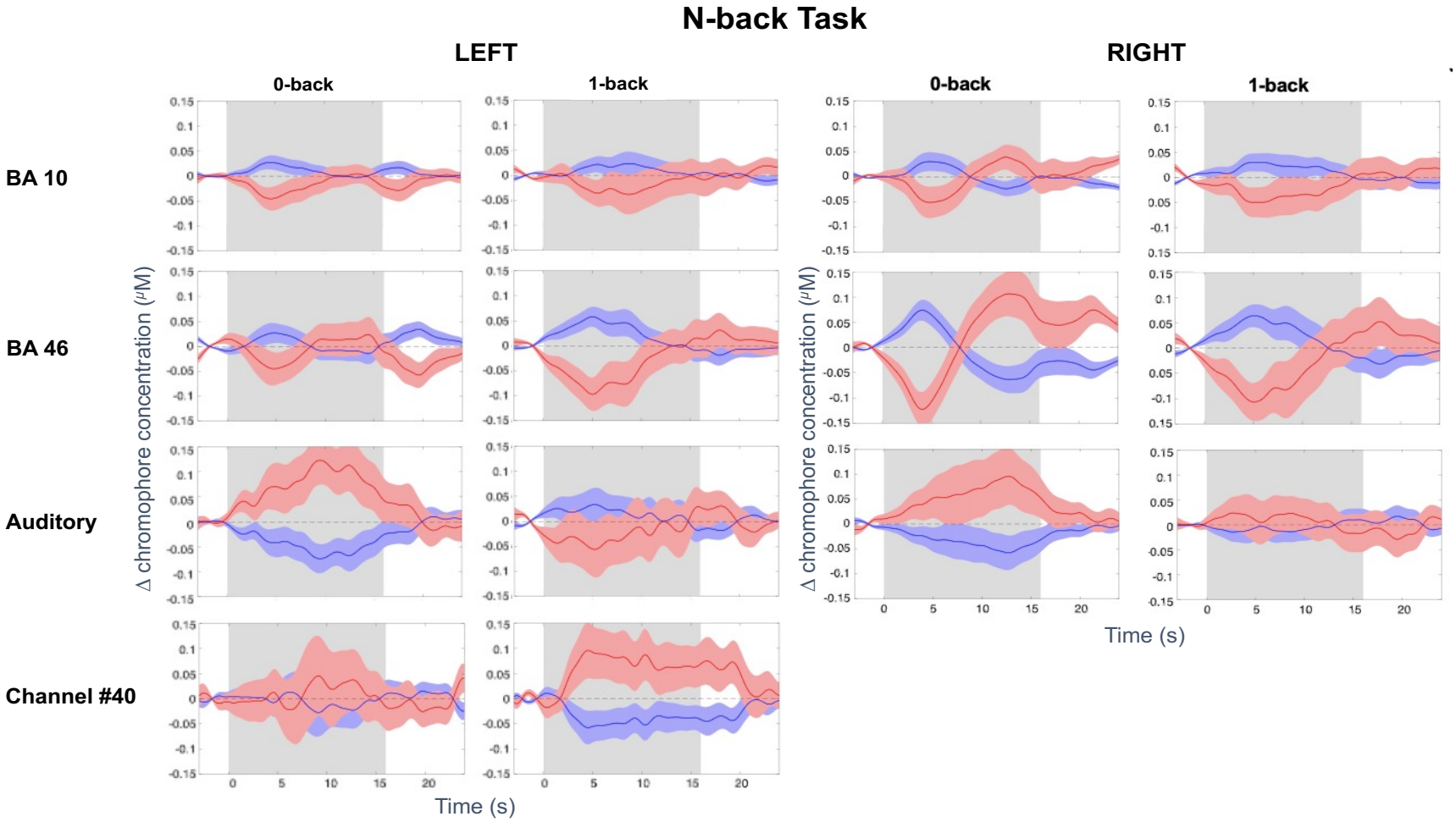


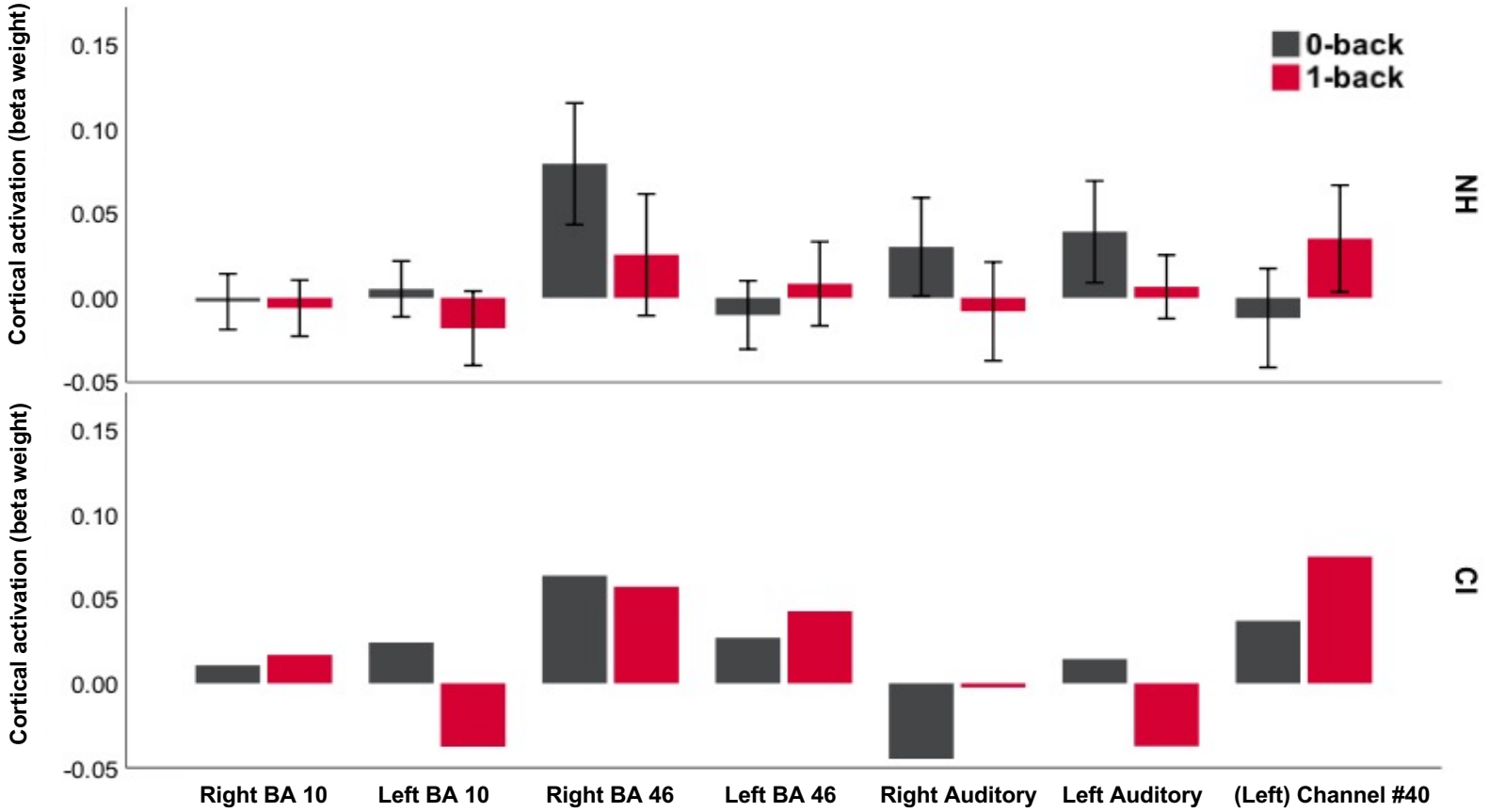
Figure 5.14: Group-averaged time courses of activation to the N-back task for NH participants. Changes in HbO and HbR concentration are shown for both the 0-back and 1-back condition of the task (compared with rest) in each of the defined ROIs. LEFT and RIGHT relate to the hemisphere in which each ROI is located. Stimulation period indicated by shaded grey region. Coloured shading indicates ± 1 SEM across participants. **n = 23.**

however, a similar response was seen in both auditory ROIs during the 0-back condition. Responses from the CI group are not included, but once again visual examination of the data showed that responses were free from device related artefacts.

Mean group level beta weights derived from each ROI during the N-back task for NH participants are shown in Figure 5.15. The beta weights for the one CI participant are also demonstrated. In NH participants, consistent with the cortical activation map and group-averaged time courses, increased activation during the 0-back condition was apparent in the right BA 46 ROI and both auditory ROIs. Conversely, channel #40 overlying left BA 44 detected an increased amplitude of cortical activation during the 1-back condition and a relative deactivation (compared to rest) during the 0-back condition. Akin to NH participants, the CI user displayed increased activation from the 0-back to the 1-back condition in channel #40. Interestingly, deactivation compared with rest was observed in the right auditory ROI during both conditions and in the left auditory ROI during the 1-back condition for this CI participant.

LMM analysis of beta weights within each ROI for NH participants that performed the N-back task is summarised in Table 5.5. The only statistically significant finding was a significant main effect of task performance ($F_{1,20}$ =5.40, p<.05) on cortical activation detected by channel #40, with increasing task performance

Figure 5.15: Bar chart showing mean amplitude of cortical activation during the N-back task for NH participants and one CI user



This bar chart shows beta weights for the NH participants (mean for n = 23 participants) and one CI user. Error bars show +1 SEM.

Table 5.5: Summary of Linear Mixed Model (LMM) analysis by Region of Interest (ROI) for NH participants performing the N-back task

a) ROI	b) Condition	c) Age group	d) Condition*Age group	e) Task performance
Right BA 10	No significant main effect ($F_{1,42}$=.04, p= .85)	No significant main effect ($F_{1,42}$ =2.21, p=.15)	No significant main effect ($F_{1,42}$ =.36, p=.55)	No significant main effect during 0-back ($F_{1,20}$ =.08, p=.78) or 1-back condition ($F_{1,20}$ =.62, p=.44)
Left BA 10	No significant main effect ($F_{1,21}$=.73, p=.40)	No significant main effect ($F_{1,21}$ =.12, p=.74)	No significant interaction ($F_{1,21}$ =.02, p=.88)	No significant main effect during 0-back ($F_{1,20}$ =.00, p=.99) or 1-back condition ($F_{1,20}$ =.30, p=.59)
Right BA 46	No significant main effect ($F_{1,42}$=1.12, p=.30)	No significant main effect ($F_{1,42}$ =.08, p=.78)	No significant interaction ($F_{1,42}$ =.28, p=.60)	No significant main effect during 0-back $F_{1,20}$ =.13, p=.74) or 1-back condition ($F_{1,20}$ =.17, p=.69)
Left BA 46	No significant main effect ($F_{1,42}$=.39, p=.54)	No significant main effect ($F_{1,42}$ =.02, p=.90)	No significant interaction ($F_{1,21}$ =1.30, p=.26)	No significant main effect during 0-back ($F_{1,20}$ =.09, p=.77) or 1-back condition ($F_{1,20}$ =.05, p=.83)
Right Auditory	No significant main effect ($F_{1,42}$=.80, p=.38)	No significant main effect ($F_{1,42}$ =.10, p=.75)	No significant interaction ($F_{1,42}$ =.10, p=.75)	No significant main effect during 0-back ($F_{1,20}$ =.45, p=.51) or 1-back condition ($F_{1,20}$ =.42, p=.52)
Left Auditory	No significant main effect ($F_{1,42}$=.82, p=.37)	No significant main effect ($F_{1,42}$ =.01, p=.92)	No significant interaction ($F_{1,42}$ =.03, p=.87)	No significant main effect during 0-back ($F_{1,20}$ =.01, p=.92) or 1-back condition ($F_{1,20}$ =.66, p=.43)
(Left) Channel #40	No significant main effect ($F_{1,21}$=1.72, p=.21)	No significant main effect ($F_{1,21}$ =.138, p=.71)	No significant interaction ($F_{1,21}$ =1.25, p=.28)	No significant main effect during 0-back ($F_{1,20}$ =.02, p=.90). Significant main effect during 1-back condition ($F_{1,20}$ =5.40, p<.05), with increasing task performance associated with a greater amplitude of cortical activation (β =.074, SE =.03, t=2.32, p<.05)

Summary of LMM analysis performed for the N-back task for each ROI shown in column **a)**. Column **b)** details any main effect of condition on beta weight; column **c)** describes any main effect of age group on beta weight; column **d)** details any interaction between condition and age group on beta weight and; column **e)** describes any main effect of task performance (dPRIME) on the beta weight during the 0-back condition and 1-back condition after accounting for variance relating to age. Significant findings are highlighted in red (p<.05).

(dRPIME) associated with a greater amplitude of cortical activation during the 1-back condition (β =.074, *SE* =.03, *t*=*2*.32, *p*<.05).

5.3.2.5 The Relationship Between Cortical Correlates of Behavioural EF and Language Performance

Bivariate correlation analysis was performed to examine for any relationship between the amplitude of behavioural EF-evoked cortical activation within each ROI and language performance. Due to the sample size of each group, this analysis was possible for NH participants only.

Table 5.6 summarises the results of the bivariate correlation analysis that evaluated the association between the beta weight value measured for each ROI during the Go/NoGo IC task and language performance. Table 5.7 also summarises the results of the bivariate correlation analysis that was performed to evaluate the same association for the N-back WM task. Bivariate correlation analysis was performed using the beta weight measured for each EF condition (NoGo and 1-back) compared to rest, and for the difference in beta weight between the EF and control condition (NoGo vs Go and 1-back vs 0-back). To perform the analyses, the twenty-three NH participants (as detailed in section 5.3.2.1) were allocated to subgroups according to whether the CCC-2 or PLS-5^{UK} language assessment was performed.

Table 5.6: The results of bivariate correlation analysis evaluating the relationship between Go/NoGo task-evoked cortical activation and language performance in NH participants

	NoGo vs Rest Condition		NoGo vs Go Condition	
	CCC-2	**PLS-5^{UK}**	**CCC-2**	**PLS-5^{UK}**
Right BA 10	r = .19, p =.54	r = .15, p =.68	r = .16, p =.59	r = -.01, p =.59
Left BA 10	T_b = .19, p =.58	T_b = .09, p =.72	r = .00, p =.10	r = .11, p =.77
Right BA 46	r = -.01, p =.98	r = .31, p =.93	r = .24, p =.42	r = -.12, p =.75
Left BA 46	r = -.14, p =.65	r = .12, p =.74	r = -.07, p =.83	r = .14, p =.69
Right Auditory	T_b = -.20, p = .36	T_b = .14, p =.59	r = -.20, p =.52	r = .03, p =.93
Left Auditory	r = -.17, p =.58	r = .13, p =.72	r = -.16, p =.60	r = .45, p =.20
(Left) Channel #8	T_b = -.14, p =.50	T_b = .09 p =.75	T_b = -.12, p =.58	T_b = .49, p<.05

Twelve participants were included in the CCC-2 subgroup and eleven participants in the PLS-5^{UK} subgroup. However, one participant in the PLS-5^{UK} subgroup had channel #8 excluded, therefore only 10 participants were included in the bivariate correlation analysis for this ROI. Significant findings are highlighted in red (p<.05).

Table 5.7: The results of bivariate correlation analysis evaluating the relationship between N-back task-evoked cortical activation and language performance in NH participants

	1-back vs Rest Condition		1-back vs 0-back Condition	
	CCC-2	**PLS-5^{UK}**	**CCC-2**	**PLS-5^{UK}**
Right BA 10	r = -.06, p =.85	r = .55, p =.10	r = .00, p =.99	r = .14, p =.69
Left BA 10	T_b = .13, p =.95	T_b = .45, p =.07	r = -.02, p =.95	r = .52, p =.13
Right BA 46	r = -.19, p =.54	r = .42, p =.23	r = -.10, p =.73	r = .15, p =.67
Left BA 46	T_b = -.07, p =.76	T_b = .63, p <.05	r = .06, p =.84	r = .34, p =.33
Right Auditory	T_b = -.01, p = .95	T_b = -.09, p =.72	T_b = .09, p =.67	T_b = -.18, p =.47
Left Auditory	r = -.21, p =.49.	r = -.18, p =.62	r = -.18, p =.81	r = .09, p =.56
(Left) Channel #40	r = -.20, p =.95	r = -.39, p =.26	r = -.31, p =.31	r = -.34, p =.34

Twelve participants were included in the CCC-2 subgroup and eleven participants in the PLS-5^{UK} subgroup. No participants were affected by channel exclusion. Significant findings are highlighted in red (p<.05).

The amplitude of behavioural IC-task induced cortical activation in channel #8 overlying left BA 46 during the NoGo compared with the Go condition was significantly associated with the PLS-5^{UK} total language score (TLS), T_b = .49, p<.05, 2-tailed, (see Figure 5.16). This beta weight value was also significantly associated with the PLS-5^{UK} Expressive Communication (EC) score (T_b = .72, p<.01, 2-tailed), yet not with the Auditory Comprehension (AC) score (T_b =.34, p=.18, 2-tailed), suggesting that expressive language was driving this association. In four out of the ten participants included in this analysis (see Table 5.6), the measured beta weight was negative in value, signifying a lower amplitude of cortical activation (or greater relative deactivation) during the NoGo compared with Go condition. However, all ten NH participants had a PLS-5^{UK} TLS of >100, hence exhibited a language score within normal limits (a standard score of 100 represents the performance of the typical child of a given age, with scores between 85 and 115 corresponding to one SD below and above the mean). These results suggest that a lower beta weight value for the NoGo compared with Go condition in left BA 46 is not necessarily a neural correlate of poor language performance in NH children, rather an increasing beta weight value for the NoGo compared with Go condition (i.e. a greater amplitude of cortical activation or a lesser degree of relative deactivation) within this brain region is associated with higher language scores in children that are already performing within clinically normal limits.

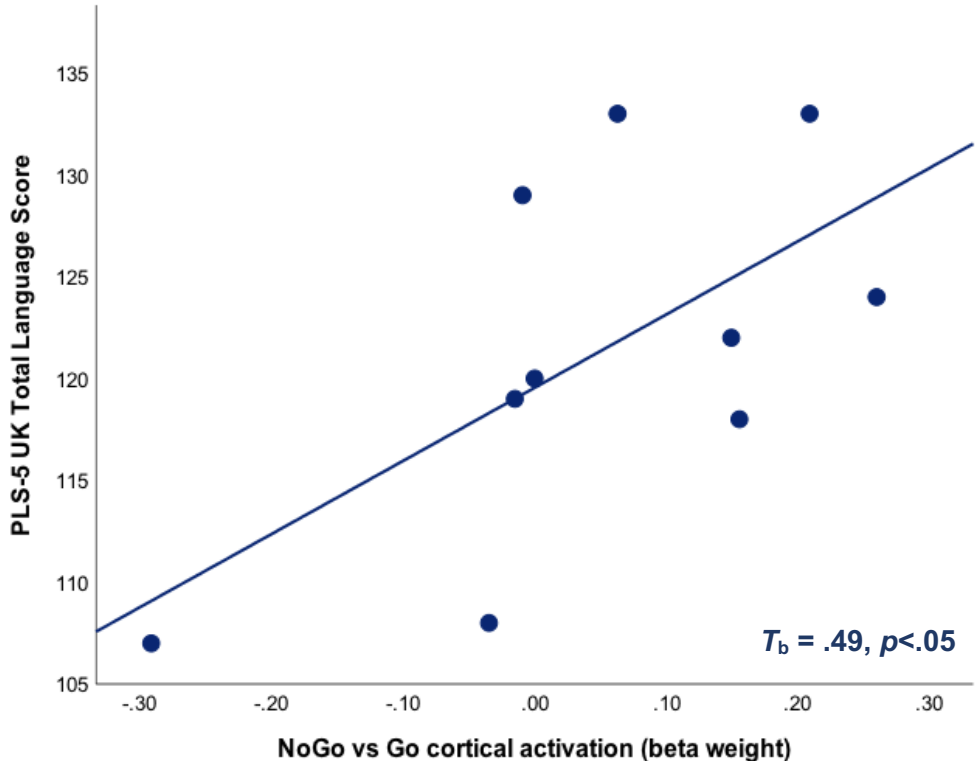


Figure 5.16: Scatterplot of the beta weight measured for the NoGo vs Go condition and PLS-5^{UK} total language score in channel #8 ROI in NH participants (n = 10).

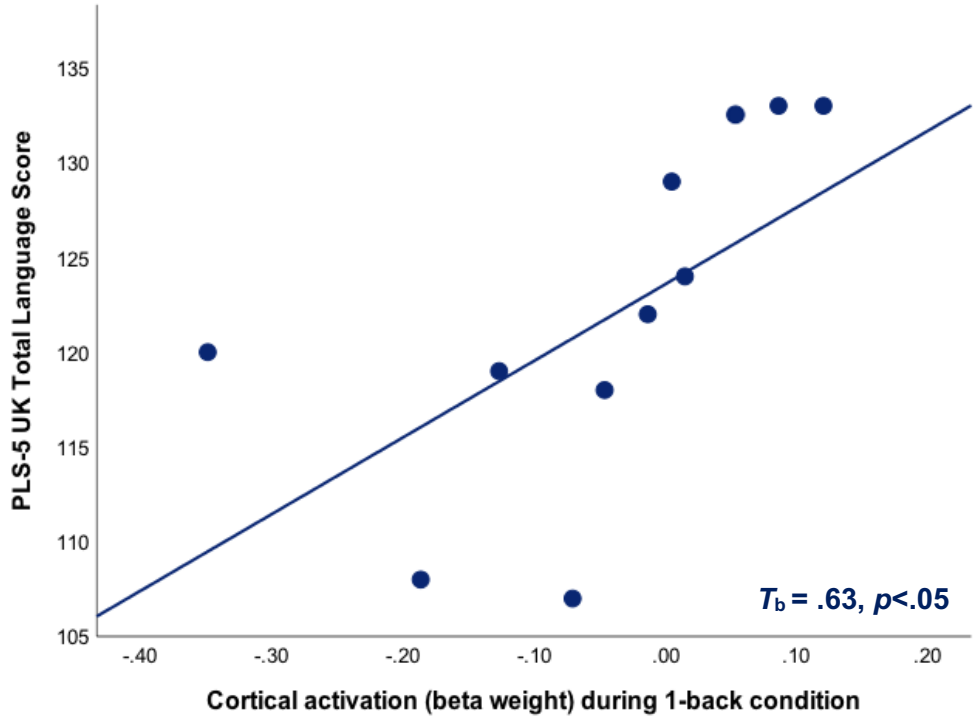


Figure 5.17: Scatterplot of the beta weight measured for the 1-back condition (vs rest) and PLS-5^{UK} total language score in the left BA 46 ROI in NH participants (n = 11).

In terms of WM, the amplitude of behavioural task-evoked cortical activation in the left BA 46 ROI during the 1-back condition when compared with rest was significantly associated with PLS-5^{UK} performance (see Figure 5.17). Interestingly, this beta weight value was significantly associated with all elements of the PLS-5^{UK} assessment (T_b = .63, p<.05 (TLS); T_b = .57, p<.05 (AC); T_b = .49, p<.05 (EC), all 2-tailed). Six participants exhibited a relative deactivation during the 1-back WM condition compared with rest, however akin to the Go/NoGo task, all these participants had PLS-5^{UK} scores within normal limits suggesting that WM task-evoked cortical deactivation (albeit relative to rest in this case) is not necessarily indicative of deficient language performance. The correlation between PLS-5^{UK} performance and behavioural EF-evoked cortical activation in all remaining ROIs (for both the Go/NoGo and N-back task) was statistically non-significant (see Tables 5.6 and 5.7). Interestingly, performance on the CCC-2 parent-reported measure was not associated with the amplitude of behavioural EF-evoked cortical activation measured across all ROIs for each of the IC and WM tasks (see Tables 5.6 and 5.7).

In terms of analysing cortical correlates of behavioural EF and their association with language performance, it is arguably more appropriate to compare the amplitude of activation measured during the EF condition (NoGo and 1-back conditions) with that acquired during the control condition (Go and 0-back), rather than with resting baseline activity. Nonetheless, regardless of the comparison

made, all statistically significant associations between behavioural EF-evoked cortical activation and language performance related to cortical correlates acquired from the left BA 46 ROI overlying the left DLPFC.

However, caution should be exercised over all findings that relate to the association between cortical correlates of behavioural EF and language ability due to the small sample sizes of the participant subgroups. As channel #8 was excluded for two participants within the PLS-5^{UK} subgroup, only ten patients were included in the bivariate correlation analysis for this ROI during the Go/NoGo task (see Figure 5.16) and only eleven subjects were included in the bivariate analysis investigating the relationship between the amplitude of N-back-evoked cortical activation in the left BA 46 ROI and PLS-5^{UK} performance (see Figure 5.17). Furthermore, the scatterplots in Figures 5.16 and 5.17 are exploratory analyses and the observed statistically significant results may have arisen simply by chance since the statistics have not been corrected for multiple comparisons.

5.3.3 Discussion

5.3.3.1 The Association between Behavioural Measures of EF and Language Performance

The first half of this chapter aimed to explore the association between behavioural measures of EF and language ability in both NH and deaf-implanted children. With respect to the relationship

between behavioural EF task performance and language, unfortunately this could not be evaluated in CI recipients due to the limited sample size. Furthermore, the onset of the COVID-19 pandemic led to a change in the assessment tool for evaluating language performance. The division of NH participants into subgroups according to the language assessment performed also resulted in small sample sizes, hence the findings within this chapter that relate to the relationship between behavioural EF task performance and language ability should be interpreted with caution. However, the parent-reported measures of behavioural EF experiment enabled a statistically powered evaluation of the association between performance on parent-reported measures of EF and language in both the NH and CI cohorts.

With respect to the relationship between behavioural performance on the IC Go/NoGo task and language ability, no significant association was observed in NH children. Conversely, parent-reported measures of behavioural IC were significantly associated with language performance, with improved IC skills tending to result in more favourable language ability in both NH children and paediatric CI users. Interestingly, the existing literature contains contradictory reports on the relationship between behavioural IC performance and language proficiency. For example, one study reported a significant association between measures of IC (using a visual continuous performance test) and language performance in NH subjects but not CI users, although it must be noted that this

study included both paediatric and adult participants (Kronenberger, Colson, et al., 2014). In contrast, language ability has been shown to be closely related to the development of behavioural inhibition in school-aged pre-lingually deaf children (Horn et al., 2005), with improved performance on a visual response delay task significantly associated with both expressive and receptive language scores. Furthermore, children implanted at a younger age tended to show a greater trajectory of improvement on this IC task over time than children implanted at an older age. Speculatively, this implies that auditory rehabilitation could lead to improvements on behavioural IC tasks that employ visual stimuli, and potentially, superior language outcome.

Akin to the IC Go/NoGo task, behavioural performance on the visuospatial WM N-back task was not associated with language ability in the NH group described in this chapter. This is inconsistent with a report that described a significant positive correlation between performance on a spatial WM task and language skills in typically-developing children (Kronenberger, Colson, et al., 2014), and furthermore, with a longitudinal study that showed superior performance on visual WM tasks to predict better language scores in NH children (Kronenberger et al., 2020). Both these studies recruited substantially more participants than the experiment described in this chapter, hence were not affected by a small sample size. Whilst the latter study also showed that measures of visual WM predicted language performance when children with CIs

were also included in the analysis (Kronenberger et al., 2020), other studies report no association between visuospatial WM and language ability in paediatric CI users (Kronenberger, Colson, et al., 2014). In terms of parent-reported measures, the current results demonstrate a significant association between WM and language performance for paediatric CI users. In contrast, no such correlation was observed in NH participants. These findings are not only in line with a plethora of reports that describe WM to be closely related to language outcome in CI users (Cleary et al., 2000; Ibertsson et al., 2009; Lyxell et al., 2008; Nittrouer et al., 2013; Wass et al., 2008; Willstedt-Svensson et al., 2004), but also with evidence demonstrating that WM plays a greater role in language functioning in CI users than their NH peers (Kronenberger et al., 2018). Interestingly, verbal WM tasks have previously shown the strongest predictive relationship with language outcome in CI recipients suggesting that phonological WM is particularly vital for encoding and processing degraded and coarsely coded speech signals transmitted via a CI device (Kronenberger, Colson, et al., 2014; Kronenberger et al., 2020). Unfortunately, the relationship between performance on a verbal WM task and language ability was not investigated in this thesis due to the available standardised assessments only being validated in children over 6 years of age. Nonetheless, despite parent-reported measures of WM providing a generic assessment of WM rather than evaluating the separate elements of visuospatial and verbal WM, the current results suggest that parent-reported measures acquired via the BRIEF tool have the

potential to detect deficiencies in WM that are significantly associated with less favourable language performance in paediatric CI users.

In addition, the current results demonstrate that global (GEC) BRIEF scores correlated with language ability in both NH and CI participants, an association that was significantly stronger for CI recipients. This finding supports evidence that language development has a greater dependence on behavioural EF in paediatric CI users, a claim based on the hypothesis that EF regulates listening effort (Pichora-Fuller et al., 2016). As described earlier, challenging listening conditions associated with the degraded auditory input of a CI device demand additional effort be allocated to listening and language processing. Deaf-implanted children with more favourable EF are perhaps more efficient at dedicating such additional effortful resources to listening, hence explaining their tendency to exhibit superior language outcome.

Interestingly, the current results also revealed that there was no significant association between parent-reported measures of EF and performance on specific behavioural EF tasks in NH children. However, this association was only evaluated using two behavioural EF tasks, the Go/NoGo and N-back tasks. Since COVID-19 substantially affected participant recruitment and the original face-to-face testing schedule of these experiments, limited sample sizes prevented analyses of the relationship between parent-reported

measures of EF and other behavioural tasks such as the A-not-B, tongue and mommy/me tasks in both NH and deaf-implanted children.

5.3.3.2 Capability of fNIRS to Detect Behavioural EF-evoked Cortical Activation

The current results appear the first to confirm that fNIRS is capable of successfully measuring artefact-free haemodynamic responses to behavioural EF over bilateral frontal and superior temporal regions in paediatric CI recipients. Although there are number of established fNIRS studies that have demonstrated the capability of fNIRS to acquire cortical correlates of behavioural EF in typically-developing children (Baird et al., 2002; Buss et al., 2014; Gu et al., 2018; Mehnert et al., 2013; Perlman et al., 2016; Smith et al., 2017), the vast majority have examined EF-evoked cortical activation over frontal and/or parietal regions without consideration of the temporal cortex. Specifically, the results within this chapter confirm the suitability of fNIRS for evaluating cortical correlates of behavioural EF within the predefined region of the left and right superior temporal cortex of NH children of preschool age. Whilst activation across the group of NH children was non-significant after one-tailed *t*-tests and subsequently correcting for multiple comparisons across 52 measurement channels, the topographical patterns and time courses of activation demonstrate the measurement of behavioural EF-evoked activation over lateral prefrontal and superior temporal brain regions. Furthermore, there was evidence of substantial

between-subject variability in the amplitude of behavioural EF-evoked cortical activation across all defined ROIs. The finding of EF-induced cortical activation in channels overlying the left superior temporal cortex of NH participants is particularly interesting since the stimuli within the behavioural tasks did not contain an auditory element.

Although statistical testing with one-tailed *t*-tests failed to identify any significantly activated channels, subsequent LMM analysis indicated significant EF-evoked cortical activation in certain channels i.e. a significant main effect of condition for the Go/NoGo task in Channel #8 as discussed in further detail below. These differences potentially relate to the necessary adjustment for the multiple comparisons following the one-tailed *t*-tests, which may have tipped any findings into insignificance. Speculatively, a larger sample size may have yielded different conclusions. As described in section 3.5.4, the EF ROIs aimed to measure EF-evoked cortical activation overlying BAs 10 and 46. However, due to the anatomical extent of these BAs (as highlighted in Figure 2.4), it is difficult to determine if specific locations within each BA are more functionally relevant for EF processing. For example, 'Channel #8' and the predefined 'left BA 46 ROI' were both measured to overlay left BA 46, yet in anatomically distinct regions. However, LMM analysis indicated a significant main effect of condition for the Go/NoGo task in the 'Channel #8' ROI, but not the 'left BA 46' ROI which consisted of three fNIRS channels. Therefore, it could also be argued that being

more specific with ROI selection, in terms of the number and location of channels included in each ROI, may also have determined the statistical significance of the current findings.

In terms of the Go/NoGo task, the current finding of substantial EF task-evoked cortical activation over lateral prefrontal areas of NH children during both the Go (control) and NoGo (inhibition) conditions is consistent with existing paediatric fNIRS studies (Mehnert et al., 2013; Smith et al., 2017). These established studies have shown that typically-developing children of preschool age exhibit a greater amplitude of fNIRS detected cortical activation over lateral prefrontal areas during Go trials than older children (Smith et al., 2017) and adults (Mehnert et al., 2013). A possible explanation for this finding is that, in comparison with older children and adults, younger children require greater attentional effort and demand a higher WM load to remember when to react to a target stimulus and when not to react to a non-target stimulus during both task conditions. This hypothesis is supported by the current results which demonstrate increased cortical activation over bilateral BA 46 of both NH participants and the one CI user during both Go and NoGo conditions. Brodmann Area (BA) 46 is commonly accepted to be located within the DLPFC, a region of the brain that has been consistently associated with WM processing (Buss et al., 2014; Perlman et al., 2016; Ullman et al., 2014). Furthermore, the DLPFC has been specifically implicated in the active maintenance of information within WM, which functions to keep information

available ‘online’ for the purpose of achieving task goals that are typically of low difficulty (Cohen et al., 1997; Mehnert et al., 2013; Smith et al., 1996), such as remembering when to respond and when not to respond during the Go/NoGo task. The bilateral DLPFC is also reported to be the main correlate of the central executive, which as detailed in section 2.3.2, is hypothesised to exert overall control over WM processes (Baddeley, 2003; Cohen et al., 1997; Gu et al., 2018). As discussed later in this chapter, more challenging WM processes that require encoding, manipulation and retrieval of information appear particularly dependant on ventrolateral rather than dorsolateral regions of the PFC (Baddeley, 2003; Cohen et al., 1997; Gu et al., 2018).

Channel #8, which was retrospectively found to overlay left BA 46 within the DLPFC (albeit in a more posterior and dorsal anatomical position than the predefined left BA 46 ROI), detected a significantly greater amplitude of cortical activation during the NoGo condition compared with the Go condition in NH participants. This channel also detected a substantial increase in cortical activation from the Go to the NoGo condition in the CI user. Interestingly, in NH participants this effect appears to have been driven by children of a lower chronological age due to a statistically significant interaction between the NoGo condition and age younger than 4.9 years. Conversely, older NH children displayed significantly greater cortical activation during the NoGo condition compared with the Go condition in the right hemisphere, specifically in the BA 10 ROI. As

already described, the literature commonly accepts that BA 46 is located within the DLPFC (Badre, 2008; Perlman et al., 2016; Smith et al., 2017). The anatomical location of BA 10 is more controversial, with numerous fNIRS reports describing it to be part of the VLPFC (Perlman et al., 2016; Smith et al., 2017), whilst other neuroimaging reports deem it a separate entity named the 'lateral orbitofrontal cortex' or 'lateral frontopolar cortex' (Badre, 2008). If for the purposes of this chapter the location of BA 10 is accepted to be within the VLPFC, then the current results align with existing reports from fNIRS, fMRI and MEG studies that show IC task-induced activation to increase with age within the right VLPFC of typically-developing children (Durston et al., 2006; Mehnert et al., 2013; Vara et al., 2014), and decrease with age in the left DLPFC (Durston et al., 2006; Vara et al., 2014).

Although no fNIRS studies examining behavioural EF-evoked cortical activations within the temporal cortex of NH children or paediatric CI users could be identified in the literature, the current finding of substantial IC-induced activation over superior temporal regions of NH participants is consistent with reports from fMRI (Liddle et al., 2001; Vara et al., 2014; Vidal et al., 2012) and MEG (Vidal et al., 2012) studies conducted in typically-developing adolescents and adults. Whilst the current results demonstrate NH children aged over 4.9 years to have a significantly greater amplitude of cortical activation in the left auditory ROI during the NoGo inhibition condition, all the aforementioned established neuroimaging studies

observed IC-induced activation in superior temporal regions to be right-lateralised (Liddle et al., 2001; Vara et al., 2014; Vidal et al., 2012). However, all children that participated in the current fNIRS experiments were substantially younger than subjects included in these established neuroimaging studies. It is therefore feasible that IC task-evoked cortical activation in superior temporal brain regions varies according to developmental stage, akin to the current observations for behavioural IC-induced activation over lateral prefrontal brain regions. The current statistically significant finding of a greater amplitude of IC-induced cortical activation over the left auditory ROI in older children therefore warrants further investigation in future fNIRS studies.

Although it is impossible to make definitive between-group comparisons due to the sample size of the CI group, it is worth noting that the CI participant exhibited substantially less IC-induced activation in bilateral auditory ROIs than the mean amplitude of activation measured for NH participants during the Go/No-Go task. This observation comes with the caveat that the CI participant was younger (4.3 years) than the mean age for the NH participants (5.2 years, SD 0.75) and had lower performance accuracy in terms of dPRIME (1.35) than NH subjects at the group-level (mean 2.13, SD 1.43). However, in support of this finding of lower IC-evoked cortical activation in superior temporal regions of the CI participant, LMM analysis failed to show a significant main effect of task performance on the beta weight value acquired for the NoGo

condition in NH participants. It is intriguing that the current findings raise the possibility that behavioural IC-evoked cortical activation in bilateral prefrontal regions is similar for NH and deaf-implanted children, yet differs between these two cohorts in superior temporal brain regions.

With respect to the visuospatial N-back task, although statistically non-significant, substantial activation was observed during the control 0-back condition in the right BA 46 and bilateral auditory ROIs of NH participants. The finding of an increased amplitude of cortical activation in channels overlying the DLPFC (albeit right-lateralised within the BA 46 ROI) during the 0-back condition adds further support to the previous theory that children recruit this region of the cortex even during control conditions of EF tasks. The CI user that performed the N-back task also exhibited increased cortical activation over the DLPFC during the 0-back condition, although in this participant, increased activation was observed within the BA 46 ROI bilaterally. Interestingly in all participants, the amplitude of cortical activation over the DLPFC tended to be greater during the 0-back condition compared with 1-back condition. This is finding is inconsistent with the paediatric fNIRS study conducted by Smith et al. (2017), which despite employing the exact same paradigm as the current N-back experiment, reported cortical activation to significantly increase from the 0-back to the 1 back condition throughout prefrontal brain regions. However, participants in the Smith et al. (2017) study were not only older on average

than participants in the current N-back experiment described in this chapter, but they also had superior group-level task performance (higher mean dRPIME score). These observations are noteworthy since Smith et al. (2017) demonstrated that both age and task performance had a significant effect on the amplitude of 1-back induced activation within bilateral prefrontal brain regions. A significant main effect of task performance on the amplitude of cortical activation during the 1-back condition was similarly observed in the current N-back experiment, albeit only in channel #40 overlying left BA 44, yet age was found to have no effect on WM task-induced cortical activation.

Consistent with reports from existing fNIRS (Smith et al., 2017) and fMRI (Braver et al., 1997; Cohen et al., 1997) studies, substantially increased cortical activation from the 0-back to 1-back condition was detected by channel #40 overlying left BA 44 within the VLPFC of NH participants. This finding was also observed in the paediatric CI user. With respect to NH subjects, this replicates evidence from established fMRI studies (albeit adult studies) that report a significantly increased left-lateralised signal in BA 44 during the 1-back condition of a visually presented sequential-letter task (Braver et al., 1997; Cohen et al., 1997). Neuroimaging evidence has indicated that the phonological loop component of WM is primarily located within the left temporoparietal region (Baddeley, 2003), with the articulatory rehearsal component specifically localised to left BA 44 (Baddeley, 2003; Cohen et al., 1997; Paulesu et al.,

1993). Numerous established studies have shown that participants are able to successfully recode visual stimuli during EF tasks, which through the process of articulatory rehearsal, subsequently gain access to the phonological loop (Baddeley, 2003; Brandimonte & Gerbino, 1993; Horn et al., 2005). Therefore, it is feasible that the substantial cortical activation observed over left BA 44 in the current experiment is accounted for by participants recoding the visuospatial stimuli to verbal material, which is then subsequently and continually used to sub-vocally rehearse when to respond to a target stimulus during the N-back task.

The increased amplitude of EF-evoked activation that was observed overlying left BA 44 may also reflect attentional resources dedicated to the behavioural WM task. Brodmann area 44, along with BA 45, forms Broca's area that is specifically located within the left inferior frontal gyrus (LIFG), a cortical region already identified as a possible neural correlate of effortful listening through its implication in the processing of degraded auditory input (White & Langdon, 2021; Wijayasiri et al., 2017; Wild et al., 2012). However, a previous adult fNIRS study from our laboratory demonstrated that the LIFG only exhibited an elevated response to degraded speech when attention was directed towards the stimulus (Wijayasiri et al., 2017). An increased amplitude of WM-evoked activation overlying the left BA 44/LIFG of the current participants may therefore actually be more indicative of the amount of attention paid to the

task, since the current experiments used visual and not auditory based tasks.

With respect to 1-back induced fNIRS responses overlying superior temporal regions of NH participants, the mean beta weight value measured for the left auditory ROI represented an increased amplitude of cortical activation from resting baseline. Conversely, mean deactivation compared with rest was observed within the right auditory ROI. Working memory-evoked cortical activation within temporal brain regions is not a novel finding. A recent paediatric fNIRS study, which notably recruited older participants (mean age 7.4 years) than the current experiment, demonstrated increased cortical activation in the bilateral superior temporal cortex of typically-developing children during the 1-back condition of a visual N-back task (Gu et al., 2018). Furthermore, an adult fMRI study reported 1-back induced cortical activation within the right superior temporal gyrus during a visual N-back WM task (Cohen et al., 1997). The current findings are therefore somewhat aligned with established, albeit limited neuroimaging studies, that demonstrate cortical activation within superior temporal regions of NH subjects during behavioural WM tasks employing visual stimuli. However, once again, the NH participants recruited to the current experiment are younger than those in established studies. Hence, it is not possible to make direct comparisons in terms of the laterality of this WM-evoked activation within the superior temporal cortex.

Although an increased amplitude of cortical activation was observed within the left auditory ROI of the CI participant during the 0-back condition, the amplitude of this detected activation was substantially less than the mean value for the NH group. Furthermore, cortical deactivation compared to rest was observed in both auditory ROIs of the CI participant during the 1-back condition. Akin to the results for the Go/NoGo task, these findings for the N-back task raise the possibility that WM-evoked cortical activation is of a lower amplitude in deaf-implanted children than their NH peers. Once again however, this between-group comparison is merely descriptive and comes with the caveat that only one CI user participated in the N-back experiment. Furthermore, the CI participant was not only younger than the mean age for the NH group, but also exhibited inferior task performance (dPRIME 1.39) when compared with NH participants (mean dPRIME 2.52, SD 1.07). Since Smith et al. (2017) reported 1-back evoked cortical activation to increase with age and task performance, these participant characteristics cast an element of doubt over the suggestion deaf-implanted children exhibit lower WM-evoked cortical activation within superior temporal regions compared with their NH peers. At the time of writing this thesis, no studies relating to WM-evoked cortical activation within temporal regions of deaf-implanted children were available for comparison.

5.3.3.3 The Association between Cortical Correlates of Behavioural EF and Language Performance

The current study provides the first known report of a statistically significant association between cortical correlates of behavioural EF and language performance in NH children. Interestingly, despite substantial behavioural EF-evoked cortical activation having been observed in bilateral prefrontal and auditory ROIs, only the amplitude of left hemispheric prefrontal activation was significantly associated with language performance. Specifically, performance on the PLS-5^{UK} language assessment significantly correlated with visual IC and WM task-evoked activation within the left BA 46 ROI overlying the DLPFC. However, these results must be interpreted with caution since the analyses performed were exploratory in nature and the lack of corrections for multiple comparisons indicates there is a possibility that these significant observations occurred by chance alone. Nonetheless, as already stated, the DLPFC is reportedly the neural correlate of the central executive (Baddeley, 2003; Cohen et al., 1997; Gu et al., 2018). Baddeley & Hitch's (1974) model of WM not only reports the central executive to represent the overall attentional control of WM, but it also infers that it is neuronally connected to the visuospatial sketchpad and phonological loop (see section 2.3.2). An increased amplitude of cortical activation within ROIs overlying bilateral DLPFC was observed during the current Go/NoGo and N-back experiments, suggesting that both these tasks demand an element of WM. It seems feasible that when the central executive is recruited to

dedicate the required attentional control to these EF tasks, cortical activation within the DLPFC leads to increased neuronal activity within the visuospatial sketchpad and phonological loop via established neuronal connections of the WM system. As the phonological loop is commonly accepted to be located within the left temporoparietal region (Baddeley, 2003; Vallar et al., 1997; Warrington et al., 1971), one potential explanation for the left auditory ROI activation during the current Go/NoGo and N-back experiments is via top-down neuronal influence from the recruited DLPFC.

Children who dedicate greater attentional control to visual EF tasks, and more actively recruit the central executive within the DLPFC, are perhaps also more likely to allocate such effortful resources to other tasks such as those involving listening and language. This hypothesis would explain the current finding of a significant association between visual EF task-evoked cortical activation within the left DLPFC and language outcome. It also raises the possibility that superior temporal regions may not be implicated in the processing of visually-based IC and WM stimuli, with behavioural EF task-induced activation within auditory areas occurring merely because of top-down influence from a recruited DLPFC. Conversely, adult fMRI literature has already demonstrated a role for both prefrontal and temporoparietal regions in verbal WM processing in NH subjects (Emch et al., 2019). Furthermore, a recent fNIRS study showed that in response to increasingly challenging listening

conditions, adults recruit numerous frontal brain regions including the left DLPFC which suggests that listening effort is somewhat reliant on higher cognitive auditory attention and WM mechanisms (White & Langdon, 2021). Interestingly, this study also found that listening effort is driven by a voluntary allocation of attentional resources, which lends support to the previous theory that children who allocate more attention to visually-based EF tasks are likely to voluntarily pay greater attention to listening and language acquisition. It would have been interesting to include a verbal WM task in the current experiments not only to examine behavioural performance, but also whether any verbal WM task-evoked cortical activation in prefrontal and auditory ROIs correlated with language outcome. However, as mentioned earlier, no verbal WM assessment tools are currently validated for the age of children recruited to the experiments within this chapter.

The current results also raise the possibility that deaf-implanted children display similar patterns of visual IC and WM-evoked cortical activation within prefrontal brain regions, however, exhibit a lower amplitude of activation within superior temporal regions. This hypothesis needs to be investigated with an appropriately powered study. However, should this hypothesis prove correct, it may be explained by the decoupling of auditory from prefrontal brain regions, a phenomenon that has previously been demonstrated in congenitally-deaf cats (Barone et al., 2013). If neuronal decoupling of these two brain regions occurs in severe-to-profoundly deaf

children, then less top-down causal neuronal influence from prefrontal to auditory areas during EF tasks seems likely. However, as already described, the current results suggest that language outcome correlates with the amplitude of visual IC and WM-evoked cortical activation overlying left prefrontal regions only. It is therefore feasible that any deficient top-down neuronal connectivity from prefrontal to auditory regions, which would potentially result in a lower amplitude of visual IC and WM task-evoked activation within superior temporal regions, would not be associated with adverse language outcome. However, if Baddeley & Hitch's (1974) model of WM is considered, then deficient neuronal connectivity between prefrontal and temporoparietal regions would disrupt verbal WM processes that are already accepted to be closely associated with language processing and acquisition (Baddeley, 2003; Emch et al., 2019; White & Langdon, 2021). This would also provide an explanation for why behavioural performance on verbal WM tasks is a stronger predictor of language outcome than performance on visual WM tasks in CI recipients, an interesting finding not observed amongst NH children (Kronenberger, Colson, et al., 2014; Kronenberger et al., 2020).

An alternative hypothesis for the lower amplitude of visual IC and WM-evoked activation in superior temporal regions of deaf children compared with NH peers is the process of cortical re-organisation (Sharma et al., 2009). Decoupling of prefrontal and auditory areas in deaf children may make superior temporal regions more available

to other modalities outside of EF stimuli. If auditory areas are specifically implicated in EF processing, then take over by other stimuli may render superior temporal regions less active during EF tasks. Considering the current results, this explanation seems less likely since there was no correlation between the amplitude of EF task-evoked activation in superior temporal regions and language outcome. However, future experiments with larger numbers of CI participants would enable a further examination of these hypotheses, since the association between the amplitude of behavioural EF-evoked cortical activation and language outcome was performed for NH participants only.

5.4 CHAPTER SUMMARY

The results of this chapter are aligned with the existing literature that reports behavioural measures of EF to be significantly associated with language performance in both NH and deaf-implanted children. Parent-reported measures of global EF were found to significantly correlate with language ability in both cohorts of children. This association was significantly stronger in children with CIs compared with their NH peers. Performance on behavioural EF tasks was not associated with language ability in NH children, a finding inconsistent with established evidence. However, this observation may relate to the sample sizes associated with the current behavioural experiments, which were typically smaller than those described in the literature.

In keeping with the aims of this thesis, this chapter has demonstrated the successful application of fNIRS in measuring artefact-free behavioural EF-evoked cortical activation within predefined bilateral prefrontal and superior temporal regions of NH children and paediatric CI users. Importantly, the current chapter provides the first investigation of the relationship between cortical correlates of EF and language ability. A significant association between the amplitude of visual IC and WM task-evoked cortical activation overlying the left DLPFC and language performance was observed in NH participants. Increasing cortical activation in such prefrontal regions may represent a child's ability to dedicate greater attention and effort to a variety of behavioural tasks, including those involving listening and language. This theory would explain why language performance was found to correlate with visual EF-evoked activation in prefrontal regions only.

Although a finding that needs to be interpreted with caution (due to the associated sample size), the current results raise the possibility that the amplitude of visual EF-evoked cortical activation within superior temporal regions of deaf-implanted children is lower than that observed for NH peers, whilst the amplitude of activation within prefrontal regions is comparable between the two groups. This observation may relate to neuronal decoupling and hence deficient connectivity between prefrontal and superior temporal regions, a phenomenon that reportedly occurs after a period of auditory deprivation in animal models, leading to less top-down neuronal

influence from higher-order prefrontal regions. Neuronal decoupling between these cortical regions may be particularly problematic for verbal WM processing, as evidence suggests that such processing mechanisms are dependent upon both these cortical areas. Verbal WM is reported to have the strongest predictive relationship with language ability in paediatric CI users, which raises the question as to whether the strength of connectivity between prefrontal and superior temporal regions may contribute to variance in CI language outcome. The next chapter examines this theory in further detail.

6. CORTICAL CONNECTIVITY AS A PREDICTOR OF FUTURE EXECUTIVE FUNCTION AND LANGUAGE PERFORMANCE

6.1 INTRODUCTION

This chapter aimed to investigate whether fNIRS measures of cortical connectivity can help predict future EF and language outcome. This evaluation primarily focused upon NH children since the small sample size associated with CI participants prevented formal statistical analysis in the paediatric CI user group. The first part of this chapter reports resting-state connectivity as a potential predictor of EF and language performance. Regression analyses were used to assess the extent to which fNIRS measures of resting-state connectivity between prefrontal and superior temporal regions can help explain variance in EF and language ability observed amongst infants and children. The second part of this chapter examines cortical connectivity on EF task-evoked brain activation. Again, regression analyses were employed to assess the ability of such connectivity between prefrontal and superior temporal areas to predict later EF and language performance. Aligned with the aims of this thesis, the longitudinal development of both resting-state connectivity and connectivity on EF task-evoked cortical activation is also discussed in this chapter.

6.2 RATIONALE

Throughout typical development, prefrontal brain regions establish both intrinsic and extrinsic neuronal connections to form the EF

system (Fiske & Holmboe, 2019). Evidence from infant MRI studies shows that structural markers of connectivity, such as gray and white-matter characteristics, are able to predict later cognitive (Deniz Can et al., 2013) and language performance (Short et al., 2013). EEG coherence is considered a valid measure of functional cortical connectivity (Broomell et al., 2019). Resting-state fronto-temporal EEG coherence measured in infants has already been shown to predict toddler inhibition, which in turn predicts later communication ability (Broomell et al., 2019).

Although resting-state connectivity between frontal and temporal regions of typically-developing infants has previously been examined with fNIRS (Bulgarelli et al., 2020), the longitudinal experiment within this thesis is the first to examine the relationship between fNIRS measures of cortical connectivity and language performance. As discussed in Chapter 2, fNIRS has been employed to evaluate resting-state connectivity in the auditory-deprived brain (McKay et al., 2016). However, only one adult subject was examined in this study. Furthermore, no assessment of the association between resting-state connectivity and language was performed, and inter-hemispheric rather than fronto-temporal resting-state connectivity was evaluated. With respect to connectivity analysis on EF task-induced cortical activation measured with fNIRS, this has already been investigated in numerous paediatric studies (Buss et al., 2014; Buss & Spencer, 2018; Mehnert et al., 2013). Although improvement in EF

performance was accompanied by greater fronto-parietal connectivity in all these studies, the relationship between connectivity and language development was not examined. Additionally, these studies focused on connectivity between prefrontal and parietal cortices, without consideration for temporal regions. Although fronto-parietal connectivity is recognised as being important for the development of behavioural EF, there is currently no existing evidence to implicate a relationship between connectivity between these specific brain regions and language performance. Conversely, as already detailed, Broomell et al. (2019) report that fronto-temporal EEG coherence can predict EF performance, which is subsequently predictive of future communication skills. It is for this reason that the current chapter concentrates on the ability of resting-state fronto-temporal connectivity, and fronto-temporal connectivity on EF task-induced brain activation, to predict both EF and language performance. Intra-hemispheric fronto-temporal connectivity (i.e. connectivity between left prefrontal and left superior temporal regions, and right prefrontal and right superior temporal regions) is specifically examined as this has been the commonly adopted approach in studies that have examined the relationship between measures of functional connectivity and EF and/or language performance (Broomell et al., 2019).

Established EEG evidence suggests that EF task performance is less favourable when top-down connectivity from prefrontal to parietal regions is weak (Perone et al., 2018; Putman et al., 2014). In the

current experiments, Phase Transfer Entropy (PTE) was employed to determine both the strength and direction of fronto-temporal connectivity. This analysis enabled an examination of whether any connectivity found to be predictive of EF and/or language performance was due to either top-down or bottom-up neuronal processes.

6.3 ANALYSES

6.3.1 Resting-state Connectivity

For each participant at each testing session within the longitudinal experiment, resting-state connectivity between intra-hemispheric ROIs overlying prefrontal and superior temporal brain regions was quantified using a PTE value. These PTE values were calculated by firstly computing causality between all pairwise channels during the 5 minute period of resting-state data (see section 3.3.3.1). Subsequently, a PTE value that reflected connectivity between two specific ROIs was quantified by averaging the PTE values for the relevant pairwise channels within those ROIs. Since PTE estimates the causal influence one cortical region exerts over another, it not only provided a measure of the strength of connectivity between two defined ROIs, but also enabled the direction of connectivity to be determined.

In each regression analysis, the PTE value for each ROI pairing at the T0 session was defined as the predictor variable. The dependent variables included the BRIEF GEC *T* score as a measure of EF performance and the relevant age-appropriate parent-reported

measure of language ability. Data for both these dependent measures were acquired as close as possible to 12 months after the T0 session. The BRIEF GEC score was selected as the outcome measure for EF performance as: 1) *T* scores provided standardisation for age, and; 2) experiments detailed in Chapter 5 of this thesis have shown that BRIEF GEC *T* scores significantly correlate with language performance (CCC-2 scores) in both NH children and paediatric CI users of preschool age. With respect to parent-reported measure of language ability, the assessment defined as the dependent variable in each regression analysis is clearly specified in the relevant sections. Prior to all statistical testing, histograms and the Shapiro-Wilk test were used to examine whether the distribution of each variable significantly differed from normality and all data were tested for the assumptions relevant to bivariate linear regression. Unfortunately, regression analyses could only be conducted for NH participants due to the small sample size of CI participants.

The evolution of resting-state connectivity over time was examined via paired *t*-tests and the results presented via group-level masked *t*-maps. Single sample, one tailed *t*-tests were conducted on the PTE values acquired for each ROI pairing at each of the T0 and T1 testing sessions. However, by testing for a significant increase in connectivity in all 52 individual measurement channels across both testing sessions, multiple comparisons are conducted and the risk of Type I error is increased. These multiple comparisons were

accounted for by applying the FDR method across channels (Benjamini & Hochberg, 1995; Singh & Dan, 2006). Statistical significance was assessed against an FDR-corrected threshold of $p<.05$. Again, this statistical analysis was only possible for NH participants.

6.3.2 Cortical Connectivity on Executive Function Task-evoked Brain Activation

To evaluate connectivity on EF task-evoked cortical activation, fNIRS data acquired during the tongue task within the longitudinal experiment were examined. The tongue task was specifically selected for this analysis as 15 NH participants performed this task at their T0 session, meaning that connectivity data could be included in bivariate linear regression models. Although the same number of participants performed the mommy/me task, the short duration of the behavioural trials associated with this task (typically under five seconds) made the acquired fNIRS data unsuitable for analysis. The lack of ability to analyse the mommy/me data related to the relatively sluggish fNIRS haemodynamic response, which typically has its onset around two seconds after the task-evoked cortical activity (Quaresima & Ferrari, 2016). Unfortunately, this limitation of fNIRS also prevented analysis of data acquired during the A-not-B task, which also consisted of short trials lasting less than ten seconds.

Like the resting-state connectivity analysis, fronto-temporal connectivity on tongue task-evoked brain activation was quantified for each participant using a PTE value. The PTE value for each defined ROI pairing was derived from fNIRS activation data that was averaged across all nine tongue task trials completed by each participant. For bivariate linear regression analyses, the PTE value at the T0 session was defined as the predictor variable, with dependent variables including the BRIEF *T* GEC score and age-standardised parent-reported language scores. Both BRIEF and language performance measures were acquired as close as possible to 12 months after the T0 session. As only one CI participant performed the tongue task, regression analysis could only be performed for the NH cohort. Relevant examinations were performed to assess whether the distribution of each variable significantly differed from normality and for bivariate linear regression specifically, all data were tested for the assumptions of this statistical methodology.

Group-level masked PTE *t*-maps were produced for NH participants with the aim of examining the change in connectivity over time from the T0 to the T1 testing session. However, as only nine NH participants repeated the tongue task, we interpret these results with caution due to the small participant sample size.

6.4 RESULTS

6.4.1 Resting-state Connectivity

6.4.1.1 Description of the Samples

Participants that performed the resting-state task within the longitudinal fNIRS experiment were included in this analysis. Table 6.1 summarises the NH sample. Tables 6.2 and 6.3 summarise the clinical characteristics and other relevant details for the sample of CI participants. Only data for NH subjects were included in formal statistical analyses. However, data acquired from the paediatric CI users is used for descriptive purposes where relevant throughout this chapter. Resting-state data were acquired for 23 NH and two CI participants at the T0 testing session. Data were not acquired for participants NH (LT)_10 and CI (LT)_02 at the T1 testing session due to a failure in the computer equipment and refusal to cooperate in the task respectively. Overall, fNIRS data were therefore available for 22 NH participants and one CI participant at the T1 session. Due to the impact of COVID-19 on the testing timeline, only two NH participants underwent a T2 testing session. For this reason, only resting-state data from the T0 and T1 sessions were included in the analysis. Furthermore, participant CI (LT)_01 withdrew from the study after their T1 session and COVID-19 prevented participant CI (LT)_02 undergoing any further testing sessions. There was no concern over the quality of

Table 6.1: Summary of NH participants included in the resting-state connectivity analysis

a) Participant ID	b) Age at T0	c) Age at T1	d) Interval between T0 and T1	e) Interval between T0 and BRIEF	f) Interval between T0 and language assessment	g) Language assessment performed	h) Length of resting-state task T0	T1
NH (LT)_01	2.8	3.4	7	14	14	CCC-2	5.0	5.0
NH (LT)_02	2.1	2.6	6	12	12	CDI-III	3.7	2.5
NH (LT)_04	1.6	2.0	5	13	13	CDI-III	5.0	5.0
NH (LT)_06	2.6	3.1	6	12	12	**	3.7	5.0
NH (LT)_07	1.0	2.4	17	13	13	CDI-WS	5.0	5.0
NH (LT)_08	3.4	4.8	17	13	13	CCC-2	5.0	5.0
NH (LT)_09	3.3	4.3	13	12	12	CCC-2	5.0	3.9
NH (LT)_10	3.0	4.0	12	12	12	CCC-2	5.0	n/a
NH (LT)_11	0.7	2.1	17	*	12	CDI-WS	2.0	5.0
NH (LT)_12	3.1	4.2	13	12	12	CCC-2	5.0	5.0
NH (LT)_13	3.7	4.8	14	13	13	CCC-2	5.0	5.0
NH (LT)_14	1.8	2.9	13	12	12	CDI-III	5.0	5.0
NH (LT)_15	2.4	3.4	12	12	12	**	4.6	5.0
NH (LT)_16	1.8	2.8	12	12	12	CDI-III	5.0	5.0
NH (LT)_17	3.3	4.4	14	12	12	CCC-2	5.0	5.0
NH (LT)_18	1.0	2.1	13	13	13	CDI-WS	5.0	5.0
NH (LT)_19	0.7	1.6	12	*	12	CDI-WS	5.0	3.0
NH (LT)_20	3.6	4.6	12	12	12	CCC-2	5.0	5.0
NH (LT)_21	2.0	3.0	12	12	12	CDI-III	5.0	5.0
NH (LT)_23	2.7	3.7	12	12	12	**	5.0	5.0
NH (LT)_24	2.0	3.0	12	12	12	CDI-III	5.0	5.0
NH (LT)_25	0.9	1.8	11	*	11	CDI-III	3.8	3.8
NH (LT)_27	2.4	3.4	12	13	13	**	5.0	5.0
Mean (SD)	**2.2 (0.96) years**	**3.2 (0.99) years**	**11.9 (3.3) Months**	**12.4 (0.60) months**	**12.3 (0.63) Months**	-	**4.7 (0.73) minutes**	**4.7 (0.71) minutes**

Column **a)** Participant ID; **b)** Age at T0 session; **c)** Age at T1 session; **d)** Time interval between T0 and T1 session; **e)** Time interval between T0 session and completion of BRIEF parent-reported measure; **f)** Time interval between T0 session and completion of parent-reported measure of language performance; **g)** Parent-reported language measure performed: CCC-2 = Children's Communication Checklist, CDI-WS = MacArthur-Bates Communicative Development Inventory-Words and Sentences, CDI-III = MacArthur-Bates Communicative Development Inventory-III; **h)** Length of resting-state data acquired at the T0 and T1 testing sessions. *BRIEF not performed for participants < 24 months old. **Language assessment not performed due to a lack of a parent-report measure validated for children aged between 38 and 47 months. NH (LT)_10 highlighted in red as no resting-state data was acquired for this participant at the T1 testing session due to a fault with the computer equipment.

Table 6.2 Summary of clinical characteristics for the CI participants included in the resting-state connectivity analysis

a) Participant ID	b) Aetiology of HL	c) Age at HL diagnosis	d) Age at CI Surgery	e) Left HT	f) Right HT	g) Additional Details
CI (LT)_01	Connexin 26 mutation	Birth	3.8	85	84	Met CI candidacy criteria at 3.2 years following revision of NICE guidance in March 2019
CI (LT)_02	Unknown	Birth	0.8	95	100	-

Column **a)** Participant ID; **b)** Aetiology of hearing loss; **c)** Age at diagnosis of bilateral hearing loss (years); **d)** Age at time of CI surgery (years); **e)** Average unaided hearing threshold (dB) for left ear across 0.5, 1, 2, 3 & 4 kHz; **f)** Average unaided hearing threshold (dB) for right ear across 0.5, 1, 2, 3 & 4 kHz; **g)** Additional relevant clinical details.

Table 6.3: Summary of details for the CI participants included in the resting-state connectivity analysis

a) Participant ID	b) Age at T0	c) Age at T1	d) Interval between T0 and T1	e) Interval between T0 and BRIEF	f) Interval between T0 and language assessment	g) Language assessment performed	h) Length of resting-state task T0	T1
CI (LT)_01	3.6	3.9	4 months	15 months	15 months	CCC-2	5.0	5.0
CI (LT)_02	0.7	1.9	15 months	16 months	15 months	CDI-WS	5.0	n/a

Column **a)** Participant ID; **b)** Age at T0 session (years); **c)** Age at T1 session (years); **d)** Time interval between T0 and T1 session; **e)** Time interval between T0 session and completion of BRIEF parent-reported measure; **f)** Time interval between T0 session and completion of parent-reported measure of language performance; **g)** Parent-reported language measure performed: CCC-2 = Children's Communication Checklist, CDI-WS = MacArthur-Bates Communicative Development Inventory-Words and Sentences, CDI-III = MacArthur-Bates Communicative Development Inventory-III; **h)** Length of resting-state data acquired at the T0 and T1 testing sessions. CI (LT)_02 highlighted in red as no resting-state data was acquired for this participant at the T1 testing session due the subject refusing to participate in the resting-state task.

the acquired fNIRS measurements, hence no exclusions were made at either the channel or participant level.

6.4.1.2 Missing Data

Although 28 NH and four CI participants were originally recruited to the longitudinal experiment (see Figure 4.1 in section 4.3.1.1), participants NH (LT)_03, NH (LT)_22, NH (LT)_26, CI (LT)_03 and CI (LT)_04 all withdrew prior to completion of the longitudinal study. Subsequently, fNIRS data and/or BRIEF and language data were not available for these subjects. Furthermore, participants NH (LT)_05 and NH (LT)_28 refused to wear the fNIRS equipment at both testing sessions. Prior to the onset of COVID-19, the plan was for every participant within the longitudinal experiment to undergo a PLS-5^{UK} language assessment. However, as described in section 3.6.2, this assessment had to be replaced by an age-appropriate parent-reported measure of language ability. It was not possible to acquire language performance data for participants that were aged between 38 and 47 months (NH (LT)_06, NH (LT)_15, NH (LT)_23 and NH (LT)_27), as no parent-reported measures are validated for this chronological age range. Furthermore, as the BRIEF-P tool is only validated for children aged $\geq$ 24 months, BRIEF data were not available for three participants (NH (LT)_11, NH (LT)_19 and NH (LT)_25). BRIEF and parent-reported measures of language data were acquired as close as possible to 12 months after the T0 session (see Tables 6.1 and 6.3). Although the aim was to achieve 5 minutes of resting-state data (see section 3.3.3.1) at each testing

session, this task was terminated early for some participants due to either irritability or distress. The amount of resting-state data (in terms of length of time) acquired for each participant at each testing session is detailed in Tables 6.1 and 6.3. Although it was possible to calculate a PTE value for each participant, the shorter length of data acquired for some subjects may have affected the accuracy of the PTE connectivity analysis.

6.4.1.3 The Ability of Resting-state Connectivity to Predict EF and Language Outcome

6.4.1.3.1 Fronto-temporal Resting-state Connectivity is Not Predictive of EF Outcome

Bivariate linear regression was performed to test whether resting-state connectivity between predefined ROIs overlying prefrontal and superior temporal brain regions was predictive of future EF outcome in NH participants (see Table 6.4). In each case, the direction of connectivity between each intra-hemispheric ROI pairing was clarified. Histograms and the Shapiro-Wilk test confirmed normality of the distribution of PTE and BRIEF data and post-hoc diagnostic measures verified that the assumptions of bivariate linear regression were met in each model: 1) a scatterplot indicated linearity between the predictor and dependent variable; 2) a Durbin-Watson test demonstrated independence of observations; 3) casewise diagnostics confirmed the absence of significant outliers; 4) visual examination of histograms and normal P-P plots indicated that the standardised residuals of the regression model were

Table 6.4: Summary of bivariate linear regression statistics for resting-state connectivity in the prediction of EF performance in NH participants

a)	b)						
Model	**Regression analyses of PTE value as predictor of BRIEF GEC *T* score (n = 20)**						
	$R^{2.}$	**Adj. R^2**	***F***	***b***	**SE *b***	***β***	***t***
Right BA 10 to Right Auditory	.00	.00	.54	-1.55	2.11	-.04	-.73
Right BA 46 to Right Auditory	.01	-.04	.24	-3.69	7.55	-.11	-.49
Left BA 10 to Left Auditory	.01	-.04	.25	54.8	-9.70	.12	.50
Left BA 46 to Left Auditory	.02	-.04	.37	-5.62	9.30	.14	.61
Left Channel 8 to Left Auditory	.02	-.04	.31	6.14	10.99	.13	.56
Left Channel 40 to Left Auditory	.00	-.06	.00	.34	9.01	.01	.04
Right Auditory to Right BA 10	.01	.05	1.91	-14.62	10.57	-.31	-1.38
Right Auditory to Right BA 46	.14	.09	2.83	-21.02	12.50	-.37	-1.68
Left Auditory to Left BA 10	.01	-.05	.11	4.01	11.92	.08	.34
Left Auditory to Left BA 46	.09	.04	1.68	-20.43	15.77	-.29	-1.30
Left Auditory to Left Channel 8	.12	.08	2.55	23.04	14.44	.35	1.60
Left Auditory to Left Channel 40	.03	-.03	.54	-6.44	8.78	-.17	-.73

Column **a)** ROI pairing included in the bivariate linear regression model, with the direction of connectivity indicated; **b)** Regression statistics for each model. The results for all models were statistically non-significant with $p > .05$.

normally distributed, and; 5) the assumption of homoscedasticity was met. The regression analyses revealed that resting-state fronto-temporal connectivity within the left and right hemisphere was not predictive of future EF outcome in NH participants (n = 20).

6.4.1.3.2 Fronto-temporal Resting-state Connectivity Predicts Language Performance

The same statistical methodology as described in section 6.4.1.3.1 was employed to examine whether PTE resting-state connectivity was predictive of future language outcome in NH participants. Regression analyses were performed with the CCC-2 (GCC score) and Mac-Arthur Bates CDI-III scores as the dependent variable in individual models. The dependent measure derived for the Mac-Arthur Bates CDI-III score was the fitted percentile score for the productive vocabulary checklist. The reasons for choosing this measure of the CDI are detailed in section 3.6.3.1. Furthermore, an established EEG study examining the relationship between resting-state connectivity and language outcome used the Mac-Arthur Bates CDI productive vocabulary checklist as the primary dependent measure (Mundy et al., 2003). Scores for the Mac-Arthur Bates CDI-WS were not subjected to regression analysis since data were only available for four participants. The results of these bivariate linear regression analyses are shown in Table 6.5. Histograms and the Shapiro-Wilk test confirmed normality of the distribution of PTE and language data and post-hoc diagnostic measures verified that the assumptions of bivariate linear regression were met.

Table 6.5: Summary of bivariate linear regression statistics for resting-state connectivity in the prediction of language performance in NH participants

a)	b)							c)						
Model	**Regression analyses of PTE as predictor of CCC-2 (n = 8)**							**Regression analyses of PTE as predictor of CDI-III (n = 7)**						
	R^2	**Adj. R^2**	***F***	***b***	**SE *b***	***β***	***t***	**R^2**	**Adj. $R^{2.}$**	***F***	***b***	**SE *b***	***β***	***t***
Right BA 10 to Right Auditory	.02	.01	2.74	12.90	7.80	.14	1.65	.00	-.01	.03	-3.24	18.45	-.02	-.18
Right BA 46 to Right Auditory	.06	-.10	.38	10.84	17.53	.25	.62	.11	-.07	.60	45.52	58.83	.33	.77
Left BA 10 to Left Auditory	.05	-.09	.33	-15.88	27.68	-.21	-.57	.19	.05	1.38	79.49	67.79	.43	1.17
Left BA 46 to Left Auditory	.01	-.16	.04	-4.44	23.0	-.07	-.19	.13	-.04	.75	69.56	80.23	.87	.43
Left Channel 8 to Left Auditory	.04	-.12	.24	-13.64	28.01	-.20	-.49	.00	-.20	.02	8.91	65.70	.06	.14
Left Channel 40 to Left Auditory	.00	-.14	.09	-1.74	19.83	-.03	-.09	.03	-.13	.21	-30.17	65.29	-.19	-.46
Right Auditory to Right BA 10	.57	.50	7.92*	57.58	20.46	.75	2.82*	.01	-.01	.42	-11.52	17.73	-.07	-.65
Right Auditory to Right BA 46	.06	-.09	.39	14.54	23.18	.25	.62	.09	-.09	.51	72.38	100.74	.30	.72
Left Auditory to Left BA 10	.15	.01	1.09	37.64	36.06	.39	1.04	.05	-.15	.25	29.94	60.89	.22	.49
Left Auditory to Left BA 46	.04	-.12	.24	-16.09	32.63	-.20	-.49	.35	.22	2.64	-141.44	87.02	-.59	-1.62
Left Auditory to Left Channel 8	.04	-.12	.25	-17.73	35.30	-.20	-.50	.35	.01	-.19	13.64	75.44	.08	.18
Left Auditory to Left Channel 40	.02	-.14	.14	-7.52	20.23	-.15	-.37	.00	-.20	.02	-10.4	74.84	-.06	-.14

Column **a)** ROI pairing included in the bivariate linear regression model, with the direction of connectivity indicated; **b)** Regression statistics for each model with CCC-2 GCC score as dependent variable; **c)** Regression statistics for each model with Mac-Arthur Bates CDI-III fitted percentile score for the productive vocabulary checklist as the dependent variable. Significantly predictive models are highlighted in red. *p<.05.

The regression analyses revealed that the PTE value for resting-state connectivity between the right auditory and right BA 10 ROI, specifically in the bottom-up direction, was significantly predictive of the CCC-2 GCC score ($F_{(1,6)}$ = 7.92, p<.05) and was able to explain 57% of the variance observed (R^2 = .57) with an adjusted R^2 of .50 indicating good generalisability of the regression model (see Table 6.5). Figure 6.1 illustrates that a positive relationship existed (Pearson's correlation coefficient r=.75, p<.05, 2-tailed), whereby NH individuals showing greater resting-state bottom-up connectivity between right superior temporal and right BA 10 regions had superior language performance on the CCC-2 parent-reported measure acquired 12 months later.

However, bottom-up resting-state connectivity from the right auditory to right BA 10 ROI was not predictive of the Mac-Arthur Bates CDI-III productive vocabulary score. Furthermore, top-down connectivity between these ROIs was not predictive of future performance on either parent-reported language measure. The remaining regression analyses revealed that resting-state connectivity between all other bilateral fronto-temporal ROI pairings was not predictive of future language outcome. Due to the limited sample sizes within each model, the findings from all these regression analyses must be interpreted with caution.

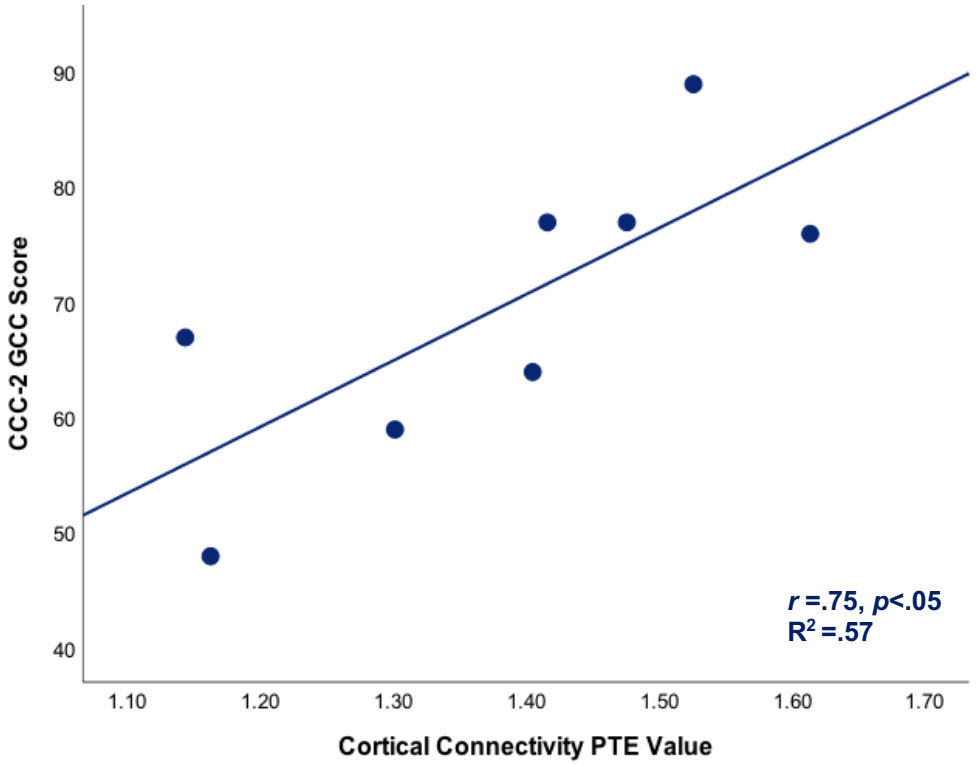


Figure 6.1: Scatterplot of resting-state bottom-up connectivity from the right auditory to right BA 10 ROI and future language outcome in NH participants (n = 8), with regression line shown. Resting-state cortical connectivity was measured with a Phase Transfer Entropy (PTE) value and language performance by the Children's Communicative Checklist (CCC-2) General Communication Composite (GCC) score.

Since the experiments within this thesis are the first to examine the relationship between fNIRS measures of cortical connectivity and language performance, there are no established fNIRS studies available for direct comparison. However, it is interesting that the current results are contrary the findings of the longitudinal EEG study conducted by Broomell et al. (2019), where increased right hemisphere fronto-temporal connectivity at age five months significantly predicted lower performance on the mommy/me inhibition task at age 24 months, which in turn predicted lower communication scores at age four years. Consequently, as a further examination, bivariate linear regression analysis was carried out

using the current data to examine whether bottom-up resting-state connectivity between the right auditory and the right BA 10 ROI measured at the T0 session was predictive of future performance on the mommy/me task, which in turn may have been associated with language performance. The PTE value for this ROI pairing at the T0 session was defined as the predictor variable, with the percentage of correct of trials on the mommy/me task at the T1 session as the dependent variable. Age at the T0 session was also entered into the model as an independent variable. Data were available for 13 NH participants. After adjusting for age, the regression analysis revealed that this PTE value was not predictive of future mommy/me performance $F_{(2,12)} = .506$, $p = .62$. The mean age of the participants at the T0 and T1 sessions was 1.9 (SD 0.69) years and 2.9 (SD 0.54) years respectively. It is important to note however, that age of participants included in the current analysis were substantially different to the Broomell et al. (2019) experiment, where participants were imaged at age five months. Hence, it is possible that the substantial difference in the chronological age of subjects in addition to the different imaging modalities used to acquire measures of fronto-temporal connectivity, may account for the opposing findings within the current results and those of Broomell et al. (2019).

6.4.1.4 The Development of Resting-state Connectivity

Figure 6.2 displays the group-level masked *t*-map that was produced to detect any significant change in PTE measured resting-

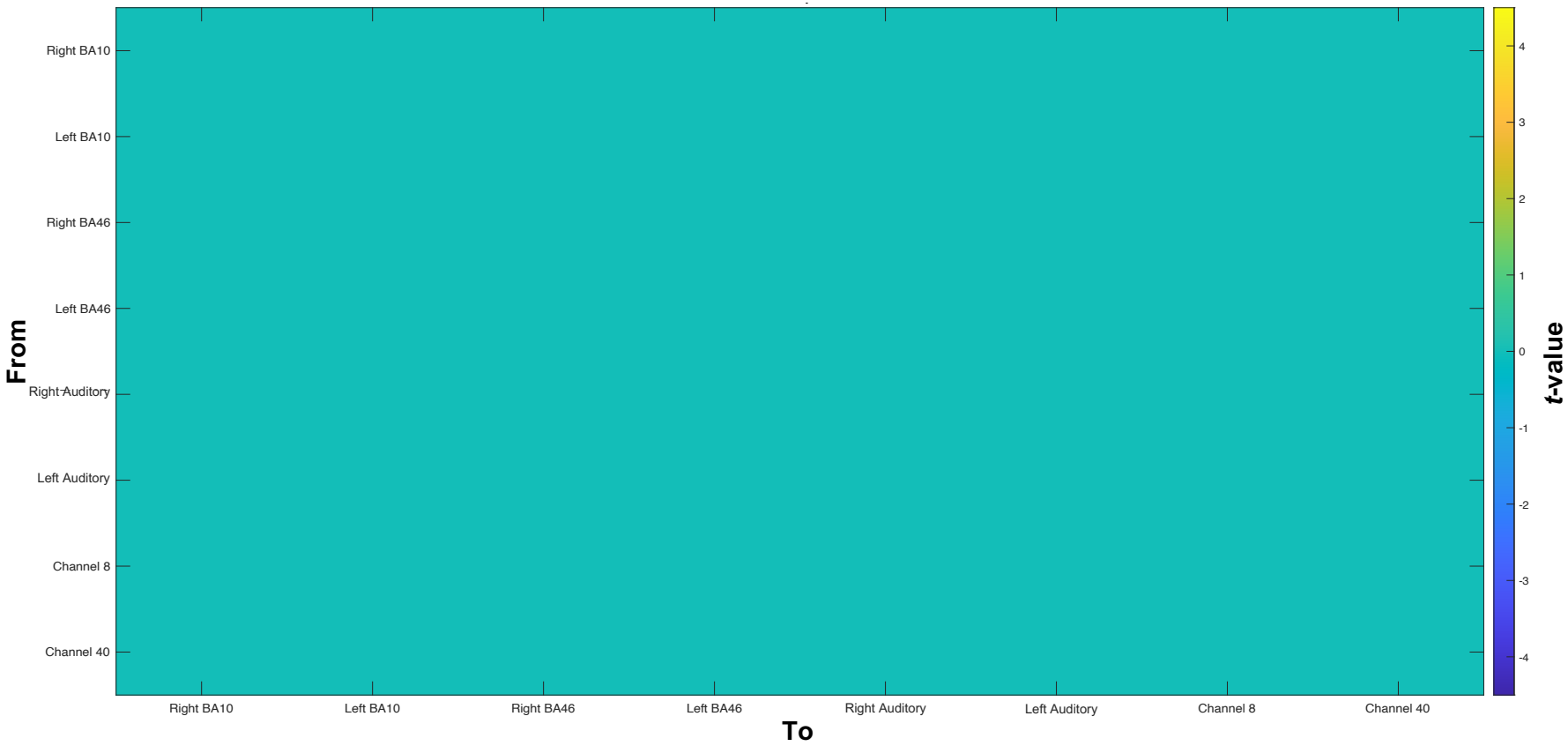


Figure 6.2: Group-level masked *t*-map for the change in the Phase Transfer Entropy (PTE) value (reflecting resting-state connectivity) from the T0 to the T1 testing session in NH participants (n = 22). Changes in the PTE value are colour coded by *t*-value (p<.05, FDR corrected), however the turquoise colour across entire *t*-map in this figure means that no significant change in the resting-state connectivity occurred between any of the ROI pairings from the T0 to the T1 testing sessions. The brain region driving the connectivity is represented on the y-axis, whilst the x-axis represents the region that tends be influenced.

state connectivity between ROI pairings from the T0 to the T1 session. Data for 22 NH participants were analysed. The mean time between testing sessions was 11.9 (SD 3.3) months. The turquoise colour across the entire map equates to a *t*-value of zero. Hence no significant change in PTE connectivity was observed between any of the ROI pairings from the T0 to the T1 testing session.

Unfortunately, it was not possible to formally evaluate the effect of cochlear implantation on the development of resting-state connectivity since only one CI participant repeated the resting-state task. Nonetheless, the PTE value reflecting bottom-up connectivity between the right auditory and the right BA 10 ROI (that was shown to predict language outcome in NH participants) did increase for the CI participant in the four month interval between the T0 to the T1 session, during which this subject received their bilateral CI devices. However, the PTE values for the right auditory and the right BA 10 ROI pairing in this CI participant were not substantially different to those acquired for NH participants of a similar chronological age, despite this CI user having a lower CCC-2 GCC score and higher BRIEF *T* score than all the NH subjects.

6.4.2 Cortical Connectivity on Executive Function Task-evoked Brain Activation

6.4.2.1 Description of the Samples

Data were available for 15 NH participants that performed the tongue task at the T0 testing session within the longitudinal

Table 6.6: Summary of NH participants included in the connectivity on tongue task-evoked brain activation analysis

a) Participant ID	b) Age at T0 tongue task session	c) Age at T1 tongue task session	d) Interval between T0 and T1 tongue task session	e) Interval between T0 tongue task session and BRIEF	f) Interval between T0 tongue task session and language assessment	g) Language assessment performed
NH (LT)_01	2.8	3.4	7	14	14	CCC-2
NH (LT)_02	2.1	2.6	6	12	12	CDI-III
NH (LT)_06	2.6	3.1	6	12	12	**
NH (LT)_08	3.4	*	*	13	13	CCC-2
NH (LT)_09	3.3	*	*	12	12	CCC-2
NH (LT)_10	3.0	4.0	12	12	12	CCC-2
NH (LT)_12	3.1	*	*	12	12	CCC-2
NH (LT)_13	3.7	*	*	13	13	CCC-2
NH (LT)_15	2.4	3.4	12	12	12	**
NH (LT)_17	3.3	*	*	12	12	CCC-2
NH (LT)_20	3.6	*	*	12	12	CCC-2
NH (LT)_21	2.0	3.0	12	12	12	CDI-III
NH (LT)_23	2.7	3.7	12	12	12	**
NH (LT)_24	2.0	3.0	12	12	12	CDI-III
NH (LT)_27	2.4	3.4	12	13	13	**
Mean (SD)	**2.8 (0.57) Years**	**3.9 (0.71) years**	**10.1 (2.8) Months**	**12.3 (0.62) months**	**12.3 (0.62) Months**	-

Column **a)** Participant ID; **b)** Age at T0 tongue task session; **c)** Age at T1 tongue task session; **d)** Time interval between T0 and T1 tongue task session; **e)** Time interval between T0 tongue task session and completion of BRIEF parent-reported measure; **f)** Time interval between T0 tongue task session and completion of parent-reported measure of language performance; **g)** Parent-reported language measure performed: CCC-2 = Children's Communication Checklist, CDI-III = MacArthur-Bates Communicative Development Inventory-III. *No repeat tongue task data available for these participants as they all performed the Go/NoGo and N-back tasks at their T1 session due to being $\geq$ 48 months old. **Language assessment not performed due to a lack of parent-report measure validated for children aged between 38 and 47 months.

Table 6.7: Summary of CI participants included in the connectivity on tongue task-evoked brain activation analysis

a) Participant ID	b) Age at T0 tongue task session	c) Age at T1 tongue task session	d) Interval between T0 and T1 tongue task session	e) Interval between T0 tongue task session and BRIEF	f) Interval between T0 tongue task session and language assessment	g) Language assessment performed
CI (LT)_01	3.6	3.9	4 months	15 months	15 months	CCC-2

Column **a)** Participant ID; **b)** Age at T0 tongue task session; **c)** Age at T1 tongue task session; **d)** Time interval between T0 and T1 tongue task session; **e)** Time interval between T0 tongue task session and completion of BRIEF parent-reported measure; **f)** Time interval between T0 tongue task session and completion of parent-reported measure of language performance; **g)** Parent-reported language measure performed: CCC-2 = Children's Communication Checklist.

experiment. Nine of these participants repeated the tongue task at the T1 session. One CI participant performed and repeated the tongue task over the two sessions. Tables 6.6 and 6.7 summarise the NH and CI participants that undertook the tongue task during the longitudinal experiment. Only data acquired from NH participants were subjected to formal statistical analysis, with data for the CI participant used for descriptive purposes only.

6.4.2.2 Missing Data

Language performance data was unavailable for four out of the 15 NH participants due to these subjects being aged between 38 and 47 months at the time of assessments. However, EF performance data was available for all other subjects. The withdrawal of the participants described in section 6.4.1.2 had no impact on the current analysis. There was no concern over the quality of the fNIRS measurements acquired during the tongue task.

6.4.2.3 The Ability of Cortical Connectivity on EF Task-evoked Brain Activation to Predict EF and Language Outcome

6.4.2.3.1 Cortical Connectivity on Tongue Task-evoked Brain Activation Predicts EF Outcome

Bivariate linear regression was performed to test whether cortical connectivity on tongue task-evoked brain activation between predefined ROIs overlying prefrontal and superior temporal brain regions was predictive of future EF outcome in NH participants. Regression analyses revealed that both top-down and bottom-up

Table 6.8: Summary of bivariate linear regression statistics for cortical connectivity on tongue task-evoked brain activation in the prediction of EF and language performance in NH participants

a)	b)							c)						
Model	**Regression analyses of PTE as predictor of BRIEF (n = 15)**							**Regression analyses of PTE as predictor of CCC-2 (n = 8)**						
	R^2	**Adj. R^2**	***F***	***b***	**SE *b***	***β***	***t***	**R^2**	**Adj. $R^{2.}$**	***F***	***b***	**SE *b***	***β***	***t***
Right BA 10 to Right AC	.00	-.08	.01	-1.4	12.29	-.03	-.114	.20	.09	1.82	-36.89	27.28	-.46	-1.35
Right BA 46 to Right AC	.00	-.07	.04	-3.09	15.47	-.06	-.20	.19	.06	1.44	35.37	29.50	.44	1.20
Left BA 10 to Left AC	.21	.15	3.55	-22.67	12.03	-.46	-1.88	.38	.29	4.24	-45.38	22.04	-.61	-2.06
Left BA 46 to Left AC	.25	.20	4.66	-22.74	10.53	-.50	-2.16*	.09	-.04	7.13	-19.13	22.65	-.30	-.85
Left Channel 8 to Left AC	.22	.16	3.64	-19.34	10.16	-.47	-1.91	.17	.05	1.39	-26.39	22.38	-.41	-1.18
Left Channel 40 to Left AC	.19	.13	3.04	-17.20	9.86	-.44	-1.74	.25	.14	2.32	-28.44	18.66	-.50	-1.52
Right AC to Right BA 10	.08	.01	1.10	12.76	12.16	.28	1.05	.02	-.14	.12	-9.82	28.54	-.14	-.34
Right AC to Right BA 46	.20	.14	3.32	-22.32	12.26	-.45	-1.82	.12	-.03	.79	-21.51	24.14	-.34	-.89
Left AC to Left BA 10	.32	.27	6.21	-24.22	9.72	-.57	-2.49*	.12	-.02	.85	-18.21	19.74	-.35	-.92
Left AC to Left BA 46	.12	.05	.1.70	-10.68	8.19	-.34	-1.30	.31	.19	2.69	-18.98	11.58	-.56	-1.64
Left AC to Left Channel 8	.00	-.07	.04	-3.17	15.50	-.06	-.20	.01	-.15	.07	8.97	34.12	.11	.26
Left AC to Left Channel 40	.17	.10	2.6	19.59	12.15	.41	1.61	.07	-.09	.42	19.16	29.33	.26	.65

Column **a)** ROI pairing included in the bivariate linear regression model, with the direction of connectivity indicated; **b)** Regression statistics for each model with BRIEF *T* score as dependent variable; **c)** Regression statistics for each model with CCC-2 GCC score as the dependent variable. Significantly predictive models are highlighted in red. *p<.05

connectivity between left prefrontal and left superior temporal regions was predictive of future EF performance (see Table 6.8). Specifically, the PTE value for top-down connectivity between the left BA 46 and left auditory ROI was significantly predictive of BRIEF *T* score, $F_{(1,14)}$=4.66, p<.05, and was able to explain 25% of the variance observed (R^2=.25), with an adjusted R^2 of .20 indicating good generalisability of the regression model (see Table 6.8). Histograms and the Shapiro-Wilk test confirmed normality of the distribution of PTE and BRIEF data and post-hoc diagnostic measures verified that the assumptions of bivariate linear regression were met. Figure 6.3 illustrates that a negative relationship existed (Pearson's correlation coefficient r=-.50, p<.05, 2-tailed), whereby individuals showing greater top-down connectivity between the left BA 46 and left auditory ROI had lower BRIEF *T* scores, signifying superior EF performance.

Whilst bottom-up connectivity between the left auditory and left BA 46 ROI was not predictive of EF performance, connectivity in the bottom-up direction between the left auditory and left BA 10 ROI was predictive of EF ability. Regression analysis revealed that the PTE value for bottom-up connectivity between the left auditory and left BA 10 was significantly predictive of BRIEF *T* score, $F_{(1,14)}$=6.21, p<.05, and was able to explain 32% of the variance observed (R^2=.32), with an adjusted R^2 of .27 indicating good generalisability of the regression model (see Table 6.8).

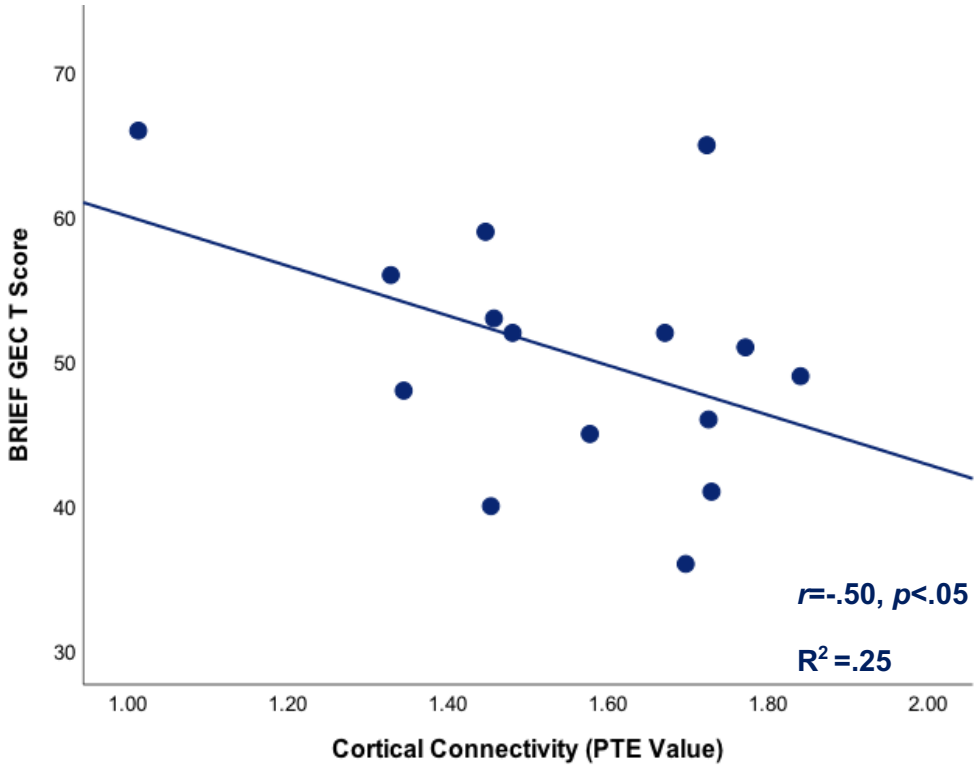


Figure 6.3: Scatterplot of top-down connectivity on tongue task-evoked brain activation from the left BA 46 to the left auditory ROI and executive function outcome in NH participants (n = 15), with regression line shown. Cortical connectivity was measured with a Phase Transfer Entropy (PTE) value and EF performance by the BRIEF GEC *T* score.

Normality of the distribution of BRIEF data for this model was confirmed. Whilst the Shapiro-Wilk test indicated that PTE data were not normally distributed, post-hoc diagnostic measures verified the assumptions of bivariate linear regression were met. Specifically, casewise diagnostics revealed there were no cases of standardised residuals greater than $\pm$3 standard deviations and the Cook's Distance statistic excluded the presence of any influential cases. Figure 6.4 demonstrates that a negative relationship existed (Pearson's correlation coefficient r=-.57, p<.05, 2-tailed), whereby participants showing greater bottom-up connectivity between the left auditory and left BA 10 ROI had lower BRIEF *T* scores, reflecting

superior EF performance. The remaining regression analyses revealed that connectivity on tongue task-evoked brain activation between all other bilateral fronto-temporal ROI pairings was not predictive of future EF outcome (see Table 6.8). Interestingly, behavioural performance on the tongue task was also not predictive of future BRIEF scores ($F_{(1,20)}$=.186, p=.67).

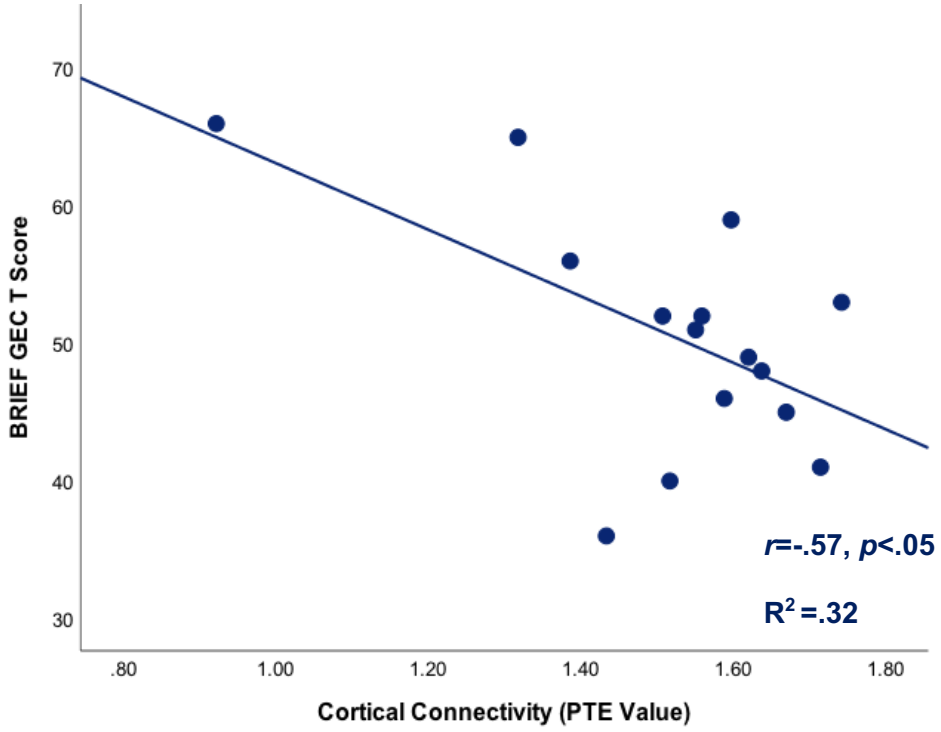


Figure 6.4: Scatterplot of bottom-up connectivity on tongue task-evoked brain activation from the left auditory to the left BA 10 ROI and executive function outcome in NH participants (n = 15), with regression line shown. Cortical connectivity was measured with a Phase Transfer Entropy (PTE) value and EF performance by the BRIEF GEC T score.

6.4.2.3.2 Cortical Connectivity on Tongue Task-evoked Brain Activation is Not Predictive of Language Performance

Bilateral linear regression analyses were performed to test whether fronto-temporal connectivity on tongue-task evoked brain activation could predict future language outcome in NH participants. Only CCC-2 performance data were included in this regression analysis as a dependent variable, hence data for eight NH participants were available. Since only three NH participants underwent a Mac-Arthur Bates CDI-III assessment, these data were not subjected to regression analysis. The regression analysis revealed that connectivity on tongue task-evoked brain activation between all bilateral fronto-temporal ROI pairings was not predictive of future language outcome measured via the CCC-2 assessment (see Table 6.8). However, despite bivariate correlation analysis revealing no significant correlation between BRIEF GEC *T* and CCC-2 score in the current cohort of eight NH participants (Pearson's correlation coefficient r=.08, p=.85, 2-tailed), the findings from Chapter 5 of this thesis demonstrated that these two parent-reported measures were significantly correlated in a larger sample of preschool age children, whereby lower BRIEF GEC *T* scores were associated with superior CCC-2 performance.

6.4.2.4 The Development of Cortical Connectivity on EF Task-evoked Brain Activation

Figure 6.5 displays the group-level masked *t*-map that was used to examine for any change in connectivity on EF task-evoked brain

from the T0 to T1 testing session. Data for nine NH participants were analysed. The mean time between testing sessions was 10.1 (SD 2.8) months. Although a significant increase in connectivity was observed between some ROI pairings, this was not the case for fronto-temporal connectivity within the left hemisphere. However, given the limited sample size here, these results must be interpreted with caution. Although it is impossible to draw conclusions for the CI cohort due to having data for only one CI participant, on a descriptive level, this paediatric CI user did exhibit an increase in the PTE value for specific left hemisphere fronto-temporal ROI parings.

These increases in PTE value occurred over four months from the T0 and T1 session, during which bilateral cochlear implantation was undertaken. Specifically, an increase in the PTE value occurred for the left BA 46 to left auditory ROI pairing (in the top-down direction) and the left auditory to the left BA 10 ROI pairing (in the bottom-up direction). It is intriguing that an increase in the PTE value for these same ROIs between was predictive of future EF outcome in NH participants. Interestingly, the PTE value reflecting top-down connectivity from the left BA 46 to the left auditory ROI was lower than all NH participants of a similar chronological age at the T0 session.



Figure 6.5: Group-level masked *t*-map for the change in Phase Transfer Entropy (PTE) value (reflecting connectivity on tongue task-evoked cortical activation) from the T0 to the T1 testing session in NH participants (n = 9). Changes in the PTE value are colour coded by *t*-value (p<.05, FDR corrected). The brain region driving the connectivity is represented on the y-axis, whilst the x-axis represents the region that tends be influenced

6.5 DISCUSSION

The current results are the first demonstrations of the capability of fNIRS correlates of fronto-temporal connectivity to predict future EF and language performance in NH infants and toddlers. Furthermore, the novel application of PTE methodology for the analysis of paediatric fNIRS data allowed the direction of any connectivity that was predictive of EF and language ability to be estimated.

In the current longitudinal experiment, resting-state connectivity between frontal and temporal regions was not predictive of future performance on either the BRIEF parent-reported measure or an EF inhibition task, however it was able to predict later language ability in NH infants and toddlers. Specifically, increasing bottom-up connectivity between the right auditory and right prefrontal (BA 10) regions significantly predicted superior CCC-2 scores. As already described, these findings contradict those of Broomell et al. (2019), whereby increased right hemisphere fronto-temporal EEG coherence during the resting-state predicted less toddler inhibition, which in turn predicted lower communication proficiency. However, the substantial difference in the age of children recruited to the current experiment and that conducted by Broomell et al. (2019), in addition to the different imaging modalities used, makes direct comparison of findings impossible.

With respect to other evidence that reports an association between resting-state connectivity and EF performance, an fMRI study

demonstrated that measures of bilateral fronto-temporal connectivity positively correlated with performance on joint attention tasks in children aged 12 and 24 months (Eggebrecht et al., 2017). However, results for fronto-temporal connectivity within each hemisphere were not individually reported in this fMRI experiment, hence it was difficult to interpret the independent effect of right and left hemispheric resting-state connectivity upon the development of joint attention skills. The central executive has been postulated as an attention system that is fundamental to the development of three core elements of EF (IC, WM and CF) (Garon et al., 2008), hence since resting-state connectivity is predictive of future performance on attention-based tasks (Eggebrecht et al., 2017), it is logical that such connectivity is also predictive of future EF performance in other domains such as inhibition (Broomell et al., 2019). The lack of ability of fNIRS correlates of resting-state fronto-temporal connectivity to predict future outcome on both the mommy/me inhibition task and the BRIEF parent-reported measure may relate to the small sample size of participants in the current experiment in comparison to other studies (Broomell et al., 2019). Further longitudinal studies analysing the relationship between resting-state connectivity and behavioural EF outcome are required for NH children. Such studies should analyse both inter- and intra-hemispheric fronto-temporal resting-state connectivity since children with ADHD and ASD, who typically have deficient EF skills, have been shown to exhibit significantly decreased inter-hemispheric frontal (Wang et al., 2020), decreased inter- and/or

intra-hemispheric temporal (Li et al., 2016; Zhu et al., 2014) connectivity in cross-sectional examinations. Research involving bilaterally severe-to-profoundly deaf children should also be conducted. Specifically, an examination of the impact that cochlear implantation has on the development of resting-state connectivity and evolution of subsequent attention and EF skills is required, as no such evidence currently exists. Unfortunately, limited recruitment to the current experiment prevented such an examination within this thesis.

The current finding that fNIRS correlates of resting-state connectivity predict language development is consistent with the results of Mundy et al. (2003) who reported that increased resting-state EEG coherence within the right hemisphere of infants aged 18 months was significantly associated with performance on the Mac-Arthur Bates CDI productive vocabulary checklist. Although Mundy et al. (2003) measured EEG coherence from frontal to central sites rather than from frontal to temporal regions, their findings in addition to the current results described in this chapter, are consistent with other studies that indicate involvement of the right hemisphere in the early acquisition of language (Blasi et al., 2011; Catani & Thiebaut de Schotten, 2008; Skeide & Friederici, 2016).

An appreciation of the cortical language network may provide an explanation for why right fronto-temporal connectivity is predictive of future language ability. Development of the cortical language

network is reported to occur in two main stages (Skeide & Friederici, 2016). In the first stage, which occupies the first three years of life, language processing is dominated by bottom-up processes that primarily enable infants to segment auditory speech input into phonological words forms (Skeide & Friederici, 2016). In the second stage, which continues into adolescence and adulthood, top-down processes emerge that facilitate increasing functional and structural connectivity of frontal regions. These top-down processes enable the integration of syntactic and semantic information (Skeide & Friederici, 2016). White-matter fibre tracts not only interconnect areas within the superior temporal cortex (STC) that are required for bottom-up language processing, but they also connect these temporal regions with frontal areas specifically involved in top-down processing (Skeide & Friederici, 2016). The arcuate fasciculus is a fibre tract that provides within-hemispheric connections between the temporal, parietal and frontal lobes (Catani & Thiebaut de Schotten, 2008) and its rate of maturation has been shown to correlate with language comprehension in preschool children (Girault et al., 2019; Skeide et al., 2016). Specifically, this tract connects the inferior frontal gyrus (IFG) with the STC and inferior parietal cortex (Sket et al., 2019). The arcuate fasciculus in the left hemisphere is typically associated with syntactic processing (Sket et al., 2019), while in the right hemisphere it reportedly has a role in prosodic processing (Catani & Thiebaut de Schotten, 2008).

In the first nine months of life, children are claimed to rely on prosody to process phonological word forms (Männel & Friederici, 2013). Furthermore, 3 year old children exhibit prosodic processing at the sentence level (Männel & Friederici, 2013; Skeide & Friederici, 2016). Since prosodic processing is considered to occur in the right hemisphere, this may explain why increasing resting-state connectivity between ROIs overlying right auditory and right prefrontal ROIs in NH infants and toddlers predicted future language performance on the CCC-2 measure in the current longitudinal experiment. Furthermore, since processing of prosodic information is initially a bottom-up process, the current finding of connectivity likely originating from right auditory areas towards right prefrontal regions is logical. However, the STC and BA 44 (within the IFG/VLPFC) are specifically implicated in prosodic processing, whereas current regression analysis showed connectivity between the right auditory and right BA 10 to be predictive of language performance. Connectivity between right superior temporal regions and right BA 44 was not specifically examined in the current resting-state experiment. Future analysis to establish whether connectivity between such areas is predictive of future language ability would be incredibly informative. Regardless, the finding that connectivity between right superior temporal and right BA 10 areas is predictive of language ability is extremely interesting since right BA 10 has already been suggested to function as the primary relay area for complex auditory information between auditory and other frontal regions, whereby activation of right BA 10 is deemed to

reflect the delegation of required attentional resources to auditory processing (Medalla & Barbas, 2014; White & Langdon, 2021).

Since infants can process basic phonological elements of speech from gestational week 28 onwards by predominantly recruiting the left STC and its connections via the arcuate fasciculus, it seems logical that the strength of left hemispheric fronto-temporal connectivity would also be predictive of future language ability, a finding not observed in the current experiment. Interestingly, Mundy et al. (2003) did find left hemisphere coherence to be predictive of language ability. Specifically, the pattern of less proximal (left frontal to left central electrodes) and more distal (left frontal to left occipital) resting-state EEG coherence in infants aged 14 months was predictive of superior vocabulary scores at age 24 months. Conversely, increased proximal EEG coherence in the right hemisphere at 18 months of age was positively associated with language performance. These results are consistent with Thatcher's theory that describes alternative patterns of maturation for the left and right hemispheres, whereby a reduction in resting-state coherence between proximal cortical sites followed by an increase in coherence between distal cortical sites occurs within the left hemisphere with advancing age (Thatcher, 1992). The opposite is reported to occur in the right hemisphere, whereby a reduction in coherence among distal cortical regions is followed by an increase in coherence among more proximal cortical areas (Thatcher, 1992).

In terms of the development of resting-state connectivity, the current results show that there was no significant change in intra-hemispheric fronto-temporal connectivity in NH infants and toddlers from the T0 to the T1 testing session, where the mean participant age was 2.2 (SD 0.96) and 3.2 (0.99) years respectively. These findings align with a longitudinal fNIRS study that reported resting-state fronto-temporoparietal connectivity to reach its maximum peak at around 24 months of age (Bulgarelli et al., 2020). Typically-developing participants recruited to this study exhibited the same number of fronto-temporoparietal connections that increased and decreased in the HbO_2 signal between 24 and 36 months of age, hence no overall increase in the strength of resting-state connectivity across the entire fronto-temporoparietal network was observed between the second and third years of life (Bulgarelli et al., 2020). Although resting-state connectivity did fluctuate amongst ROI pairings, none of the intra-hemispheric connections showed a significant change over time between 11 and 36 months of age, whereas inter-hemispheric connectivity did show a main effect of time over the same period. The increasing and decreasing connections within the fronto-tempoparietal network of participants in the aforementioned study were attributed to a pruning process, whereby redundant neuronal connections are replaced with more efficient connections (Thompson et al., 2005). This reorganisation of established functional networks aligns with Thatcher's theory on hemispheric maturation (Gao et al., 2017; Thatcher, 1992).

With regards to connectivity on EF task-evoked brain activation, the current results demonstrated that both top-down and bottom-up directed connectivity between ROIs overlying left superior temporal and left prefrontal regions of NH toddlers was predictive of future EF performance on the BRIEF parent-reported measure, yet not directly predictive of language performance on the CCC-2 tool. In contrast to the findings of Chapter 5, there was no significant relationship between BRIEF and CCC-2 scores in the current longitudinal experiment. However, the limited sample size associated with both the regression analysis that examined the ability of fronto-temporal connectivity to predict future CCC-2 scores, and the bivariate correlation analysis that evaluated the association between BRIEF and CCC-2 scores, may have influenced the current findings. The larger sample size for the regression analysis that examined the ability of connectivity on task-evoked brain activation to predict EF performance, gives a greater degree of confidence to the finding that fronto-temporal connectivity is predictive of future EF skills.

A plethora of studies using established neuroimaging techniques including fNIRS and fMRI have previously demonstrated that fronto-parietal connectivity on EF task-evoked brain activation is associated with measures of behavioural EF (Alcauter et al., 2014; Buss & Spencer, 2014, 2018; Ezekiel et al., 2013; Mehnert et al., 2013; O'Hare et al., 2008; Perone et al., 2018). However, the current findings are the first known evidence that fNIRS correlates

of fronto-temporal connectivity can predict future EF performance in NH toddlers. It is interesting that fronto-temporal connectivity on IC tongue task-evoked activation within the left, rather than right, hemisphere was predictive of future BRIEF performance. Furthermore, this left hemispheric connectivity was estimated to be both top-down and bottom-up in direction according to PTE analysis, a finding that is consistent with existing evidence stating that EF and language processing are bidirectionally related (Alderson-Day & Fernyhough, 2015; Doebel et al., 2018; Rönnberg et al., 2008). As described throughout the literature review in Chapter 2, a reciprocal relationship reportedly exists between EF and language. Components of EF are claimed to regulate efficient listening, leading to more effective language acquisition that in turn supports the achievement of goal-directed behaviour characteristic of EF (Kronenberger et al., 2020). Since the majority of language processing occurs in the left hemisphere (Skeide & Friederici, 2016), its perhaps not surprising that increased bidirectional connectivity between ROIs overlying the left STC and left prefrontal areas was found to predict more favourable EF in the current longitudinal experiment. However, if a bidirectional and reciprocal relationship does exist between EF and language, then left-hemispheric fronto-temporal connectivity would also be expected to predict language outcome. However, as already mentioned, fronto-temporal connectivity (on tongue task-evoked activation) within the left hemisphere was not predictive of CCC-2 scores in the current experiment which potentially relates to the fact that data for only

eight participants were included in the regression analysis. Furthermore, Chapter 5 demonstrated that BRIEF and CCC-2 scores were significantly associated in a larger cohort of NH children of preschool age. Since fNIRS correlates of left hemisphere fronto-temporal connectivity on EF task-evoked activation are predictive of future BRIEF scores, which are in turn associated with CCC-2 performance, fNIRS acquired fronto-temporal connectivity patterns could help relevant healthcare professionals to identify NH children who are at risk of less favourable language outcome.

With respect to the anatomical location of the fronto-temporal connectivity that was predictive of future EF, this was estimated to occur between the left BA 46 and left auditory ROIs, and between the left auditory and left BA 10 ROIs. The finding that increasing top-down driven connectivity between left BA 46 and left auditory regions during the IC tongue task predicts superior EF performance aligns with the results detailed in Chapter 5. Findings from the cross-sectional experiment revealed that increasing IC and visual WM task-evoked cortical activation in the left BA 46 ROI was significantly and positively associated with language performance in preschool aged NH children. A greater amplitude of cortical activation in the left auditory ROI was also observed during these same tasks, although activation in this region was not statistically significant and did not correlate with language outcome. One hypothesis for these observations was that increased activation within left BA 46 signified increased recruitment of the central

executive within the DLPFC, which subsequently led to top-down activation of left temporal regions via established neuronal connections. Increased recruitment of the central executive was postulated to reflect the dedication of greater attention to the EF task at hand. It was further hypothesised that the ability to allocate increased attention to a task may extend to and support listening processes, hence explaining the association between IC and visual WM task-evoked left BA 46 activation and language performance. The findings relating to fronto-temporal connectivity on EF task-evoked brain activation in the current chapter demonstrate that greater top-down and bottom-up connectivity between EF and language processing regions predicts superior EF performance (BRIEF scores) in preschool aged NH children, that in turn is significantly and positively associated with language performance (CCC-2 scores). The finding that increased top-down connectivity between the left BA 46 ROI overlying the DLPFC and the left auditory ROI was able to predict superior EF performance aligns with the adult fNIRS study by White et al. (2021) which demonstrated that attention and verbal WM mechanisms processed by the left DLPFC regulate listening effort. The current results combined with the findings of White et al. (2021) support the hypothesis that top-down connections from the left DLPFC to the left STC facilitate language acquisition, hence superior language outcome, via the regulation of auditory attention. The bottom-up connectivity that significantly predicted EF performance was between the left auditory and left BA 10 ROIs. Although EF task-

evoked activation in this prefrontal region was found to be non-significant in the cross-sectional experiments, a role for this cortical area in EF processing has previously been demonstrated in other paediatric fNIRS studies (Perlman et al., 2016; Smith et al., 2017). This further supports the finding that increased bottom-up connectivity from left superior temporal to left BA 10 regions of the prefrontal cortex predicts EF performance, which is subsequently associated with language performance.

Regarding the development of connectivity on IC tongue task-evoked brain activation, findings are once again overall consistent with the fNIRS study by Bulgarelli et al. (2020). Over the duration of the longitudinal experiment, no significant change in intra-hemispheric fronto-temporal connectivity was observed in children aged over 2 years, except for one ROI pairing (right auditory and right BA 10). It must be appreciated however, that Bulgarelli et al. (2020) specifically analysed resting-state fronto-temporoparietal connections, and it is feasible that connectivity on EF task-evoked cortical activation utilises different and/or additional neuronal networks. Furthermore, connectivity on EF task-evoked brain activation within the entire fronto-temporoparietal network needs to examined since established evidence states that connectivity between frontal and parietal cortices also mediates early EF development (Fiske & Holmboe, 2019).

Resting-state connectivity and connectivity on EF task-evoked brain activation between prefrontal and superior temporal cortices of deaf children remain inadequately investigated since recruitment of CI participants to the current longitudinal experiment was adversely affected by the COVID-19 pandemic. Descriptive analysis of connectivity data acquired from a CI participant, both pre- and post-implantation, suggested that measures of left hemispheric fronto-temporal connectivity were weaker for this CI user compared with NH peers. Future studies with larger sample sizes to examine fronto-temporal connectivity in deaf infants, and the impact of cochlear implantation on such connectivity, are required.

6.6 CHAPTER SUMMARY

This chapter provides the first known investigation of resting-state connectivity, and connectivity on EF task-evoked cortical activation, between prefrontal and superior temporal regions and the ability of each to predict future EF and language performance. Phase transfer entropy was employed for the purpose of connectivity analysis and allowed the direction of connectivity that was predictive of EF and language ability to be estimated. Analysis of resting-state data acquired from NH infants and toddlers revealed that bottom-up connectivity between right superior temporal and right prefrontal regions was predictive of language performance. Furthermore, both top-down and bottom-up connectivity on EF task-evoked brain activation between left prefrontal and left superior temporal regions of NH toddlers significantly predicted future EF performance, which

in turn was significantly associated with language performance. The development of intra-hemispheric fronto-temporal connectivity appears to peak at around 2 years of age in typically-developing children, indicating that connections between EF and language processing regions are mature by the third year of life. Future applications of fNIRS technology could enable NH children at risk of EF and language delay to be identified and treated at an earlier stage, leading to superior outcomes. Further research is required to establish whether fNIRS correlates of fronto-temporal connectivity in deaf children are predictive of EF and language performance, and whether cochlear implantation affects such connectivity.

7. RECOMMENDATIONS ON PERSONAL PROTECTIVE EQUIPMENT REQUIRED FOR COCHLEAR IMPLANT SURGERY DURING COVID-19

7.1 INTRODUCTION

This chapter presents data obtained from a systematic risk-based evaluation of PPE that facilitated the safe recommencement of CI surgery at NAIP within NUH NHS Trust during the COVID-19 pandemic. The broader goal of the work described in this chapter was to minimise the period of auditory deprivation in pre-lingually deaf children and reduce the risk of cochlear ossification in individuals following meningitis. Hence, in keeping with the overall aims of the thesis, the content of this chapter aimed to maximise language outcome in paediatric CI recipients. This chapter describes a preclinical experiment that involved: 1) an objective measure of mastoid drilling-induced droplet spread conducted during simulated CI surgery and its mitigation via the use of a protective drape tent, and; 2) an evaluation of three PPE configurations by otologists while performing mastoid drilling on ex-vivo temporal bones. The results of these preclinical studies led to recommendations on PPE and IPC measures that would enable the safe conduct of CI and other mastoid surgery. The implementation of these recommendations at NUH NHS Trust allowed the restart of CI surgery during the COVID-19 pandemic after a mandatory, yet brief, pause in surgical implantation lasting just under two months. Following the implementation of these recommendations, to ensure practicality of

CI surgery at the clinical (rather than preclinical) level and more importantly the safety of both patients and HCWs, an evaluation of the first ten CI and other mastoid surgeries following the recommencement of surgical CI services at NUH NHS Trust was performed, the findings of which are also detailed in this chapter.

7.2 ANALYSES

Descriptive statistics are utilised to present the findings in this chapter.

7.3 RESULTS

7.3.1 Preclinical Experiment

7.3.1.1 Objective Assessment of Mastoid-Drill Induced Contamination

During simulated CI surgery, mastoid drilling-induced contamination (a mixture of droplets, bone, blood and tissue) was observed in all directions from the drilling site (360^0), the extent of which was substantially reduced with use of the drape tent (ENT UK, 2020). Without the drape tent in situ, the contamination extended for over two metres from the drilling position and spread into areas containing the typical position of the operating surgeon, scrub nurse and anaesthetist (see Figures 7.1a, 7.2a and 7.2b). The distance of this spread was further than reported in previous studies (approximately one metre) that also simulated mastoid surgery (J. X. Chen et al., 2020; Hilal et al., 2005). The extended reach of contamination in the present study may be explained by the use of the fluorescent dye as irrigation fluid rather than impregnation of

the dye into bone (J. X. Chen et al., 2020). When the drape tent was utilised, as demonstrated in Figures 7.1b and 7.2c, contamination was confined within it.

7.3.1.2 Evaluation of Personal Protective Equipment During Simulated Cochlear Implantation

In terms of participant demographics, the age, gender and ethnicity of participants evaluating the respiratory PPE options varied substantially (see Table 7.1). There was an equal mix of male and female participants (n = 7 of each gender), an important representation considering the reported observation that the majority of PPE available through the NHS is designed for men, even though 75% of NHS HCWs are women (Pugh, 2020). Specific consideration also needed to be given to ethnic minorities because NHS workers from some black and other communities, particularly South Asia, reportedly find it difficult to achieve a good fit for respiratory PPE with even the smallest sizes being too big for some (Pugh, 2020). In this experiment, ethnicity of participants included Asian British Indian (n = 5), white British (n = 5), white other (n = 2), Asian Indian (n = 1), and Arab (n = 1).

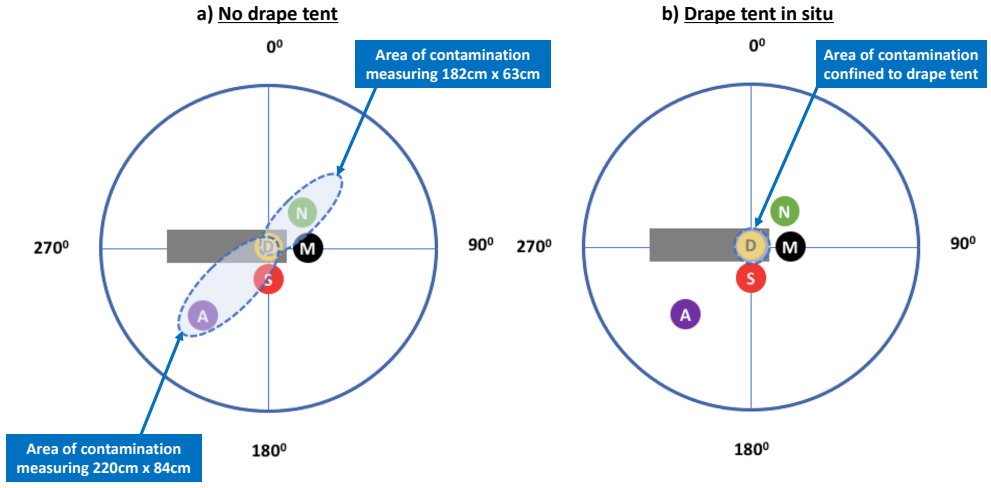


Figure 7.1: The extent of mastoid-drill induced contamination during the preclinical experiment. The grey rectangle represents the surgical operating table containing the drilling position (D) within the yellow circle. The typical relative position of the anaesthetist (A), operating surgeon (S), scrub nurse (N) and microscope (M) are also demonstrated. The areas affected by mastoid-induced contamination without and with the use of a drape tent are shown in figures **a)** and **b)** respectively. The extent of contamination in both situations is represented by the light blue shaded areas (within the blue dashed lines). The spread of the contamination encompassed the typical position of all theatre staff when the drape tent was not utilised and extended 2.2 metres at its maximum distance to the back-left and front-right of the surgeon's drilling position. However, contamination was confined to the drape tent upon the surgical operating table when the latter was in situ.

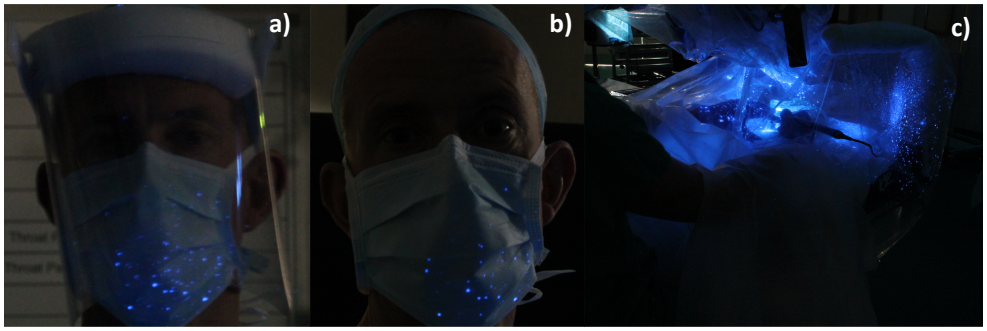


Figure 7.2: Photographic illustration of the extent of mastoid-drill induced droplet contamination during the preclinical experiment. Following a period of drilling without the use of the drape tent, contamination was visualised not only on the surgeon's visor **a)**, but also underneath it and directly onto the surgical mask **b)**. Contamination was also visualised on the floor of the operating theatre. An assessment of droplet spread following a period of drilling with the drape tent in situ revealed the visualised contamination to be contained within the tent **c)**. Also, contamination was not visualised on the surgical mask of the surgeon, nor on the floor of the operating theatre.

Table 7.1: Summary of the demographics of participants taking part in the preclinical evaluation of PPE during simulated CI surgery.

ID	Ethnicity	Gender	Age
1	White Other	Male	66
2	White British	Male	51
3	White British	Male	49
4	Asian Indian	Female	43
5	Asian British Indian	Male	43
6	Asian British Indian	Female	47
7	Asian British Indian	Male	40
8	White Other	Female	41
9	Asian British Indian	Female	35
10	White British	Female	37
11	White British	Female	34
12	Asian British Indian	Male	24
13	White British	Female	25
14	Arab	Male	36

7.3.1.2.1 Ease of Donning and Doffing

Participants were able to perform donning and doffing with ease and according to NUH NHS Trust guidelines for the full-face respirator, the full-face snorkel mask, and half-face (FFP3/2) mask with safety goggles and spoggles.

7.3.1.2.2 Efficacy of Communication

Communication between the operating surgeon and both the near (scrub nurse) and far listener (anaesthetist) for each mask type was analysed by calculating the mean percent correct score across all listeners for both AB words and sentences, each with and without the added background noise of the drill and suction. As shown in

Figure 7.3, the half-face mask (FFP3/2) provided the most efficient communication with participant's performance averaging above 75% across all conditions and listener positions. Communication was most adversely affected with the full-face snorkel mask with performance averaging 50%. The full-face respirator allowed comparatively better communication than the full-face snorkel mask, an observation more apparent for the near listener position.

7.3.1.2.3 Physiological Parameters

Analysis of the data acquired from measurements of physiological parameters during this 30 minute preclinical experiment revealed no concerning changes in HR, O_2 saturations or $ETCO_2$ levels across all participants and mask types. However, a rise in the mean $FiCO_2$ level from participants' baseline was observed for all masks except the FFP3 mask, which slightly decreased. Specifically, the substantial observed rise in the $FiCO_2$ level for the full-face snorkel mask breached current national and international health and safety regulations for respiratory PPE (see Figure 7.4), which state that inspired CO_2 levels should not rise above 1% (Morris et al., 1991; British Standards Insitution, 2002; Smith et al., 2013).

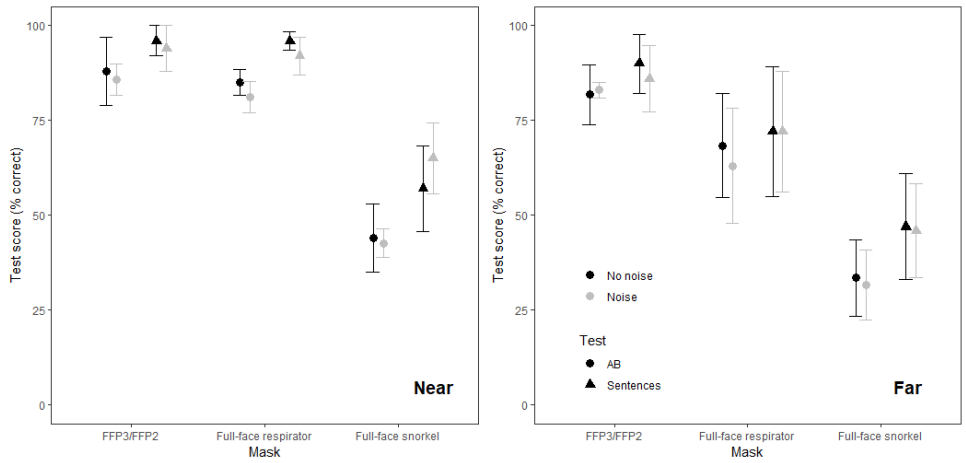


Figure 7.3: The efficacy of communication for the full-face respirator, full-face snorkel and half-face FFP3/FFP2 mask under the various listening conditions. Results are displayed separately for both near and far listeners. The data points coloured black represent % correct scores for the AB word (circle) and sentence (triangle) tests in the no noise condition. The shaded data points (in grey) represent results for the AB word (circle) and sentence tests (triangle) in the noise condition. Error bars show ± 1 SEM. The efficacy of communication for both the full-face respirator and half-face FFP3/FFP2 mask was consistently higher than the full-face snorkel mask across all listening conditions for both near and far listeners.

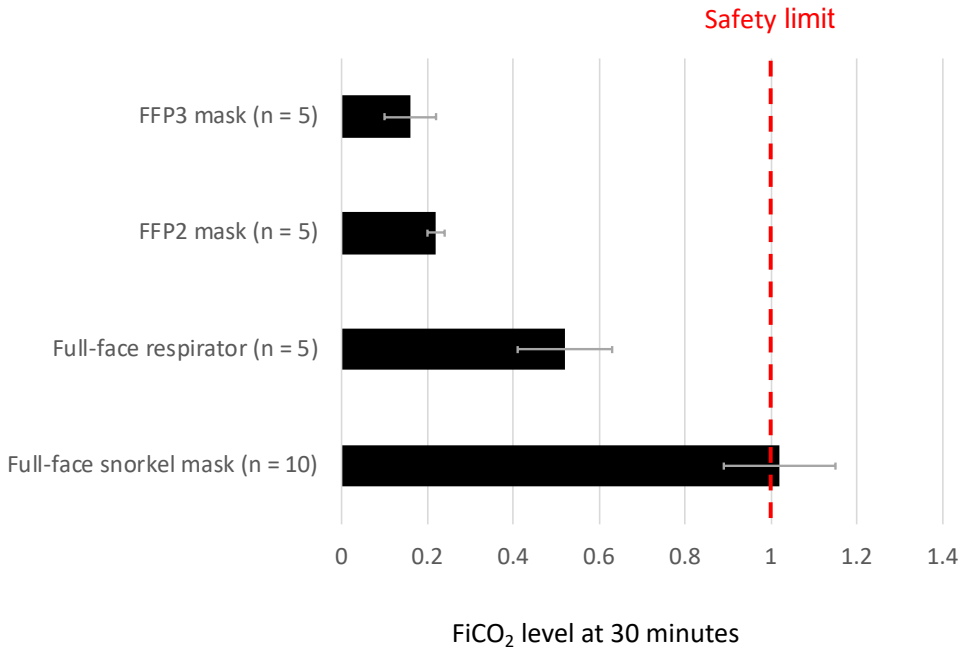


Figure 7.4. Mean participant FiCO2 levels after 30 minutes of wearing a full-face respirator, full-face snorkel and half-face FFP3/FFP2 mask. The mean FiCO2 level at 30 minutes was calculated for all participants wearing each type of mask. Error bars show ± 1 SEM. The substantial increase in FiCO2 level for the full-face snorkel mask elevated above health and safety regulations (indicated by the vertical red dashed line at 1%).

7.3.1.2.4 Subjective Comfort and Breathability

Participant reported comfort and breathability after wearing the various type of respiratory PPE for 30 minutes are shown in Figure 7.5. All participants wearing the half-face (FFP3/2) mask reported either good or adequate comfort. The comfort provided by the full-face snorkel mask and full-face respirator was reported to be inadequate by some, a higher proportion of participants reporting so for the full-face respirator. Breathability was rated as good by most participants for all types of respiratory PPE.

7.3.1.2.5 Visual Acuity and Visual Field Testing

Normal visual acuity is considered < 0.1 LogMAR, which is equivalent to a Snellen score of 20/25 feet or 6/7.5 metres. Visual acuity at 30 minutes (without use of the operating microscope) was recorded as 0.00 LogMAR for all PPE options, except for the full-face snorkel mask, where it was recorded as 0.01 LogMAR for two participants.

The effect of the different PPE solutions on the visual field was extremely variable. Figure 7.6 shows the relative reduction in the visual field (whilst using the operating microscope) caused by each type of PPE, in comparison with wearing no PPE (radius of visual field = 100%). The safety spoggles had a negligible effect upon the visual field (radius = 96%), whereas the safety goggles, full-face snorkel mask, and full-face respirator all caused a substantial

reduction of the radius of the visual field to approximately 55%, 40%, and 18% respectively.

7.3.1.2.6 Ergonomic Evaluation of PPE Solutions over Longer Periods of Time

Most participants reported that they were able to wear the full-face respirator for at least two hours, however despite this, said that they would not personally use it to perform CI surgery. Most participants trialling the full-face snorkel mask tolerated wearing it for under 60 minutes and subsequently confirmed they would not use it for CI surgery. Similarly, the combination of an FFP3 mask and safety goggles was deemed an inappropriate option by most participating surgeons. Restriction of the visual field and lack of binocular vision were major concerns for all these PPE options. The combination of a FFP3 mask and spoggles was the most popular PPE option, with all participants saying they would use it for CI surgery.

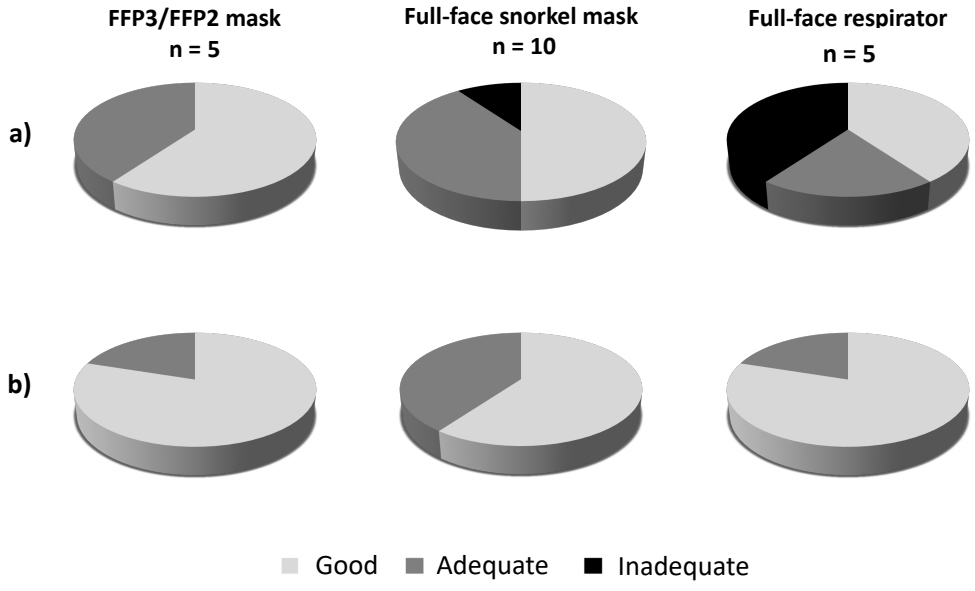


Figure 7.5: Reported participant comfort a) and breathability b) after 30 minutes of simulated CI surgery. The half-face FFP3/FFP2 mask had consistently superior performance across both subjective parameters.

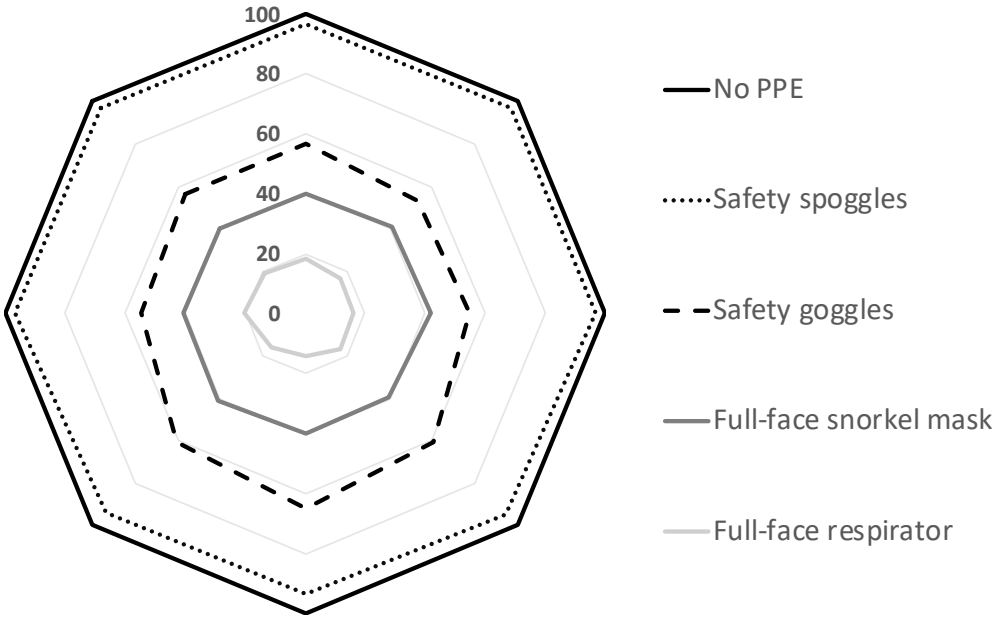


Figure 7.6: The effect of the various PPE options on participants' visual field whilst using the microscope. Each participant (n = 5) was asked to draw their visual field onto graph paper both with and without the various PPE options. The radar plot shows the mean relative reduction in the visual field caused by each type of eye PPE, in comparison to no wearing no PPE (radius of visual field = 100%).

7.3.1.2.7 Qualitative Fit Testing

All nine participants that had previously undergone qualitative fit testing for a FFP3 respirator passed with this mask type. Eight out of nine passed fit testing for the full-face snorkel mask. All five participants that underwent fit testing for the full-face respirator passed.

The findings of this preclinical study led to NUH NHS Trust recommending that CI and other mastoid surgery could be performed by surgeons wearing the combination of a FFP3 mask or

half-face respirator with safety spoggles as PPE, while also using a drape tent as an additional IPC measure. As the extent of the mastoid-drill induced contamination was also within the range of the typical position of the scrub nurse and anaesthetist, the recommendations also stated that the adequate PPE should also be considered essential for these theatre team members during mastoid drilling, and that the total number of personnel in the theatre should be kept to a minimum.

7.3.2 Clinical Evaluations of Recommended Personal Protective Equipment Following the Resumption of Cochlear Implant Surgery

7.3.2.1. Operating Surgeon Questionnaire

Five different CI/otology surgeons participated in the ten clinical evaluations. In terms of demographics, the cohort consisted of four males and one female, age ranged from 40 to 51 years and ethnicity included Asian British Indian (n = 2), White British (n = 2) and Asian Indian (n = 1). All five surgeons donned a half-face respirator in line with NUH NHS Trust recommendations (the exact type determined by availability within NUH NHS Trust and a successful qualitative fit test). Four out of the five surgeons started the surgical procedure wearing safety spoggles, hence this ocular PPE was trialled in nine out of 10 of the clinical evaluations. One surgeon was unable to wear the spoggles due to the requirement for their own personal prescription eyewear for the purpose of maximal visual acuity. The specific drape used to create the tent

depended on the IPC resources available within NUH NHS Trust at the time of each surgery, but included: 1) the standard microscope drape (Glass Lens MICRO-KOVER, Advance Medical Designs, Marietta, USA) as described in the two-microscope drape method (ENT UK, 2020) in four out of the ten clinical evaluations; 2) a CE marked drape with a custom-made hole for a secure fit over the lens cap of the standard microscope drape, also referred to hereinafter as the 'Nottingham drape tent' (intubation drape shield with endotracheal tube access, Vital Care Industries, Tinley Park, Illinois, USA), in three of the clinical evaluations, and; 3) a generic surgical drape without any customisations in the remaining three clinical evaluations (set up cover, Guardian, Girvan, Scotland, UK).

The donning and doffing of the PPE options were specifically assessed in the objective assessments (see section 7.3.2.2). In terms of changing PPE, all respondents felt it was possible to remove, change or replace pieces of the PPE ensemble without causing contamination and without doffing completely. In nine out of ten evaluations, the operating surgeon felt their donned PPE was adequately sized. In three evaluations, the operating surgeon removed the spoggles before the end of the procedure due to either intolerable discomfort (n = 2) or fogging that substantially affected visibility (n = 1). In the six evaluations where the spoggles were worn throughout the case, five respondents reported that their view of the surgical field was limited by minimal fogging but confirmed that safety was not compromised due to vision being affected to a

minimal degree only. Nine out of 10 respondents concluded that their donned PPE (either with or without the spoggles) allowed a full range of motion, dexterity and tactility required to perform CI surgery, with one surgeon reporting that discomfort had a minimal impact on all the aforementioned factors. All participants reported that communication was impaired with all other members of the theatre team, the magnitude of which was lessened by limiting unnecessary background noise. The mean operating time across the evaluations was two hours and the majority (n = 9) of surgeons experienced a degree of discomfort from their PPE ensemble at some point during surgery. One surgeon had to take a short break 90 minutes into a surgical case, but all surgeons were able to safely complete the procedure.

The two-microscope drape method (ENT UK, 2020) was used in four evaluations and two respondents using this drape reported a substantial negative effect on their view of the surgical field in addition to an adverse impact on their mobility, dexterity and tactility throughout the surgical case. The same number (n = 2) also had trouble receiving instruments from the scrub nurse on multiple occasions. All respondents that used the generic surgical drape (n = 3) and two of those using the two-microscope method (ENT UK, 2020) reported that the drape tent was repeatedly detached from the microscope. Two out of the three surgeons using the Nottingham drape tent reported that their view of the surgical field was intermittently restricted by movement of the microscope, a

problem resolved with minimal readjustment of the drape tent. Regardless of the drape tent used, sterility was maintained and macroscopic mastoid drill-induced contamination contained within the tent in all ten clinical evaluations.

7.3.2.2 Objective Assessments

7.3.2.2.1 Donning and Doffing of PPE

The donning and doffing of PPE by surgeons adhered to the NUH NHS Trust infection prevention control protocol in all ten evaluations. A visible gap in the PPE ensemble was a concern for one surgeon, with the reusable half-face respirator and spoggles an incompatible combination for this individual. A minimal gap in the fit of the ocular PPE to the face was apparent. This gap was a consequence of the superior limit of the reusable half-face respirator sitting high on the nasal bridge, which prevented an adequate seal of the spoggles. This surgeon was one of the three that removed the spoggles before the end of the surgical procedure as documented in the questionnaire assessment (see previous section 7.3.2.1). In terms of demographics, this individual was a 43-year-old Asian British Indian male who interestingly had the shortest measured distance from the nasion to the bottom of the chin across all participating surgeons. This provides a potential explanation for the reusable half-face mask reaching higher up the nasal bridge and interfering with the fit of the spoggles in this surgeon specifically, and not in others wearing the exact same reusable half-face

respirator (Force™8 Half-Mask with PressToCheck™P3 Filters, JSP®, Oxford, UK).

7.3.2.2.2 Assembly and Disassembly of Utilised Drape Tent

The time taken to assemble the drape tent was under five minutes, and the time take to disassemble was under two minutes for all utilised drapes across all ten evaluations, hence each process had a negligible effect on the total length of the surgical procedure. National guidelines for assembly and disassembly (ENT UK, 2020) were adhered to in all ten surgical cases.

In contrast to the two-microscope drape method (ENT UK, 2020) and the generic surgical drape, due to the presence of a custom-made hole, no modifications or alterations to the Nottingham drape tent were required during assembly and hence this latter drape tent was associated with the most efficient set up (see Figure 7.7). It was also apparent from this objective assessment that the Nottingham drape tent was not associated with significant 'spare' drape gathering around the surgical field (see Figure 7.8), which was a problem for the two-microscope drape tent method (ENT UK, 2020) amongst others (Carron et al., 2020; J. X. Chen et al., 2020).

7.4 DISCUSSION

The findings of the preclinical experiments presented in this chapter led to the development of recommendations on the PPE and IPC measures required to enable a safe restart of CI and other mastoid

surgery during the COVID-19 pandemic. These recommendations were implemented at NUH NHS Trust in May 2020 and the first ten CI and other mastoid surgeries (after the authorised restart of CI services) were clinically evaluated. All ten surgical cases were performed safely and successfully, hence CI and other mastoid surgery continued at NUH NHS Trust throughout the pandemic in line with The Royal College of Surgeons (RCS) surgical prioritisation guidelines (Royal College of Surgeons of England, 2020).



Figure 7.7: Assembly of the 'Nottingham drape tent'. a) custom-made hole in the CE marked sterile polyethylene drape (intubation drape shield with endotracheal access, Vital Care Industries, Tinley Park, Illinois, USA). **b)** the custom-made hole is placed over the lens cap of the standard microscope drape (Glass Lens Micro-Kover, Advance Medical Designs, Marietta, USA) to create a secure fit.

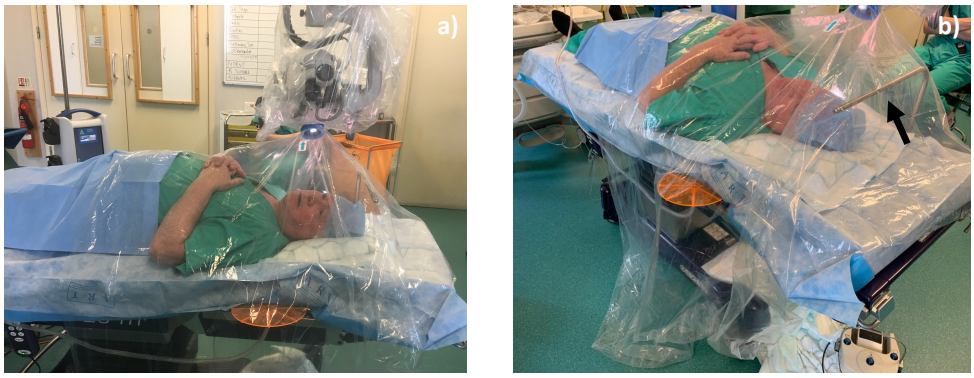


Figure 7.8: Example setup of the 'Nottingham drape tent'. The assembled drape tent, as set up for the surgical cases in the clinical evaluations, has been recreated for illustrative purposes. **a)** The CE marked sterile polyethylene drape (intubation drape shield with endotracheal access, Vital Care Industries, Tinley Park, Illinois, USA) is attached to the lens cap of the standard drape (Glass Lens Micro-Kover, Advance Medical Designs, Marietta, USA) on the operating microscope. The drape tent is then extended to cover the entire surgical field. **b)** The drape tent is supported by an 'L' support (black arrow) at the head of the patient. During CI surgery, this 'L' support was covered in a sterile endoscopic camera drape (Delta Surgical, Newcastle Under Lyme, UK). As evident from the photographs in this figure, the Nottingham drape tent was not associated with significant 'spare' drape gathering around the surgical field, a problem common to many other drape tent methods.

The preclinical objective assessment of the spread of mastoid-drill induced contamination revealed droplet contamination to extend further (up to 2.2 metres) from the drilling position than previously reported for bone scatter (Hilal et al., 2005) and particulate dispersion (J. X. Chen et al., 2020; Hilal et al., 2005). This observation formed the basis of the NUH NHS Trust implemented recommendations on the PPE required for the operating surgeon, scrub nurse and anaesthetist during CI and other mastoid surgery. A more recently performed study replicated the findings of our preclinical experiment. Markey et al. (2021) demonstrated that upon simulating mastoidectomy, splatter containing bone dust and fluid also extended over two metres from the drilling position. In addition, the authors reported that splatter distance was mitigated with the use of specific drill burrs. A 3 mm cutting burr produced

less splatter than a 5 mm cutting burr, and a 3 mm diamond burr less than either of the cutting burrs (Markey et al., 2021). However, it should be considered that surgical operating time is likely to be prolonged if smaller sized diamond burrs are used for mastoidectomy, a factor not specifically assessed in the Markey et al., 2021 study. Both the preclinical study and clinical evaluations described in this chapter have shown the use of a drape tent to be an effective way of mitigating the spread of mastoid-drill induced contamination, a finding consistent with previous reports (Carron et al., 2020; J. X. Chen et al., 2020). The clinical evaluations showed that assembly and disassembly of a drape tent had a negligible effect on the length of the surgical procedure. Objective assessments showed that the CE marked Nottingham drape tent, due to its custom-made hole and lack of required modifications to the drape, was the most efficient in terms of set up. Furthermore, surgeon feedback via the clinical evaluation questionnaire suggested advantages in surgical efficiency for this drape tent over other methods, despite an association with a minimal yet intermittent and easily reversible interruption in the view of the surgical field.

Transmission of SARS-CoV-2 virus is thought to be transmitted via either fomite, direct contact, droplet or aerosol spread (Sommerstein et al., 2020; Thamboo et al., 2020). However, the theory of transmission via aerosols has been subject to controversy (Asadi et al., 2020). At the time of writing this chapter, clinical studies had identified contamination of environmental air samples

by the RNA of SARS-CoV-2, yet without viable virus (Chia et al., 2020; Liu et al., 2020; Ong et al., 2020). The preclinical study in this chapter was designed to detect the spread of macroscopic droplet contamination only, and it is therefore impossible to draw any conclusions on the extent of drill-induced aerosolisation during simulated CI surgery from this thesis alone. Nevertheless, mastoidectomy is widely considered to be an AGP (ENT UK, 2020; Canadian Society of Otolaryngology – Head & Neck Surgery, ENT UK, 2020). Public Health England (PHE) categorises patients/individuals who are receiving medical treatment and care into high, medium and low-risk depending on: 1) their SARS-CoV-2 PCR test result; 2) the presence or absence of COVID-19 symptoms, and; 3) their COVID-19 contact/exposure status (Public Health England, 2021). Public Health England (PHE) guidance states that when AGPs are performed for medium and high-risk patients, HCWs should don either an FFP3 mask or equivalent grade reusable respirator. Adequate eye protection is considered a requirement for all AGPs by PHE (irrespective of the level of risk presented by the patient/individual) and can be either a surgical mask with an integrated visor, a full-face visor/shield or goggles. The World Health Organization (WHO) states that eye protection provided to a HCW for an AGP should achieve a good seal with the skin of the face, accommodate wearers of prescription glasses, have a clear plastic lens and even specifically lists EU standards to be that need to be met by ocular PPE (WHO, 2020). Importantly, all the PPE options within the implemented NUH NHS Trust recommendations

for the restart of CI and other mastoid surgery during the COVID-19 pandemic are compliant with PHE and WHO guidance.

The preclinical and clinical PPE assessments presented in this chapter were based on an established systematic risk-based approach to the evaluation of PPE in the healthcare setting (R. M. Jones et al., 2020). This evidence-based framework states that the categories of PPE performance that must be considered include: 1) donning, doffing, and changing; 2) usability, and; 3) fit for purpose. It was also ensured that the simulation of the activity for which the PPE was being assessed involved the relevant HCWs (R. M. Jones et al., 2020), specifically otolaryngologists in both the preclinical experiment and clinical evaluations.

In terms of donning, doffing and changing, all the aforementioned were performed with ease for all the PPE options that were subjected to a preclinical full ergonomic assessment. With respect to usability during preclinical simulated CI surgery specifically, out of the three PPE solutions that were subjected to an ergonomic evaluation, the ensemble of a half-face (FFP3/2) mask and safety spoggles had superior performance across all aspects of the evaluation. Communication was at least 80% effective across all listening conditions for this PPE ensemble, even for words spoken in isolation of any contextual cues (Figure 7.3). All participants reported comfort and breathability at 30 minutes to be good or adequate for this PPE option (Figure 7.5). No substantial changes

were observed in the vital physiological parameters measured during use of the half-face FFP3 and FFP2 masks. However, of notable concern was that despite all participants (n = 10) reporting breathability to be good or adequate for the full-face snorkel mask, a mean $FiCO_2$ level of over 1% was observed after 30 minutes (Figure 7.4). Numerous health and safety standards for respiratory PPE state the level of CO_2 in inspired air should not exceed 1% (Morris et al., 1991; British Standards Insitution, 2002; Smith et al., 2013), hence the full-face snorkel mask did not meet minimum safety standards for respiratory PPE.

The combination of eye protection with the oculars of an operating microscope has been considerably challenging (Philip Clamp, 2020), yet in the present preclinical experiment, the safety spoggles were found to have a negligible effect on the visual field (when used with the operating microscope). Although there was no detrimental effect on visual acuity, the safety goggles caused a substantial reduction in the visual field, relative to the no-PPE condition. Despite it being possible to wear safety goggles over standard corrective glasses, these preclinical findings demonstrate that this combination would substantially impair the surgeon's field of vision while using the microscope and, in some cases, may compromise the protective seal around the goggles. Furthermore, for surgeons who need to use corrective glasses to operate, prescription spoggles are available (Bollé Prescription Safety Glasses, Villeurbanne, France). The full-face snorkel and respirator caused an even greater

restriction, making all PPE options, aside from the spoggles, unsafe for microsurgery.

For PPE to be fit for purpose, it must be assessed for an adequate fit and seal to block the anticipated mode of transmission (R. M. Jones et al., 2020). The preclinical experiment found that qualitative fit testing was highly successful for all types of respiratory PPE assessed, with all participants passing for an FFP3 level mask and the full-face respirator. For the purposes of the preclinical study, qualitative fit testing was not performed for the safety goggles or spoggles. However, the specific safety goggles (Bollé Coverall COVERSI) and spoggles (Bollé BAXTER RX) used in this study both have a CE marking that indicates they provide protection against gas particles < 5 μm. Furthermore, equipment is available to objectively measure fit (3M eyewear fit system, 2021).

Preclinical findings resulted in the combination of an FFP3 mask, or half-face respirator, with safety spoggles being recommended as PPE that could facilitate the safe restart of CI and other mastoid surgery in NUH NHS Trust. The addition of a microscope drape tent was also advised. During the clinical evaluations of the first ten CI and other mastoid surgeries, all five participating surgeons wore reusable half-face respirators. All but one of these surgeons donned the safety spoggles at the start the surgical case. Donning, doffing and changing was performed without difficulty in all ten clinical evaluations.

In terms of usability at the clinical level, most surgeons felt their PPE was adequately sized. However, a gap in the reusable half-face respirator and spoggles ensemble was objectively identified for one surgeon. Furthermore, the safety spoggles had to be removed by the operating surgeon in three surgeries due to either intolerable discomfort (n = 2) or fogging that substantially affected vision of the surgical field (n = 1). Regarding those surgeons that wore the safety spoggles to the end of the case, the majority experienced minimal fogging at some point during the surgical procedure. However, this did not impact their ability to safely complete the operation. Despite the reusable half-face respirator and safety spoggles ensemble being a successful combination for some surgeons, the clinical evaluations demonstrate that a 'one-size-fits-all' approach isn't always appropriate when it comes to PPE provision.

Although PPE is often considered to be unisex (Pugh, 2020), most PPE is based on the sizes and characteristics of men from Europe and USA (Trades Union Congress, 2017). A 2016 survey conducted by numerous organisations including the trade union Prospect and the Trades Union Congress (TUC) showed that 57% of women reported PPE to either sometimes or significantly hamper their work (Trades Union Congress, 2017). The TUC provide numerous suggestions to address the issue gender inequality for PPE. These include advising employers to avoid suppliers who do not provide a range of sizes for both men and women and to ensure that any

utilised supplier has assessed the appropriateness of their PPE products to both men and women. With respect to PPE for HCWs from ethnic minority communities, in May 2020 the Royal College of Emergency Medicine (RCEM): Equity, Diversity and Inclusion Committee ran a survey to better understand the experience of its members during the first wave of COVID-19. Significantly more respondents from ethnic minorities reported that they failed fit testing for PPE: almost half (48%) of these respondents claimed that they failed fit testing either 'very often', 'often', or 'sometimes', compared to only 37% of white respondents (RCEM, 2021). In January 2021, the RCEM called upon NHS England, Senior NHS management, NHS Trust boards and other regulators to address the disparities in access to appropriate PPE for ethnic minority HCWs, a vital action armed with the knowledge that two thirds of HCWs who died in the first wave of the pandemic were from ethnic minority backgrounds (Cook et al., 2020).

In all ten clinical evaluations described in this chapter, sizing of respiratory PPE was far from problematic, with all five participating surgeons successfully passing a qualitative fit test. The challenge specifically laid in finding a PPE solution that not only provided protection from respiratory and ocular transmission of SARS-CoV-2, but was also compatible with the operating microscope. However, Jaiswal et al. (2020) representing the Scottish Cochlear Implant Centre suggest that a microscope alone (i.e. no ocular PPE) adequately shields the operating surgeon and their team from

mastoidectomy induced bone dust/droplets. This group therefore advocates that advising patients and their families to self-isolate for two weeks preoperatively, whilst also ensuring all adult patients undergo a negative COVID swab test the day before surgery, provides sufficient protection against the transmission of COVID-19 to HCWs during CI and mastoid surgery (Jaiswal et al., 2020). The authors report that their decision not to use eye protection is supported by evidence that ACE-2 receptor mRNA in corneal tissue is at between 10% and 50% of the level found in other tissues and that cofactors which allow binding of the spike protein of SARS-CoV-2 to the ACE-2 receptor on the cornea are reduced or absent (Willcox et al., 2020). It could therefore be argued that the decision to wear ocular PPE during CI and other mastoid surgery should be a personal one, which itself may be determined by interpretation of the literature and the level of risk an individual HCW is willing to accept. However, it must be remembered that electing to not wear adequate ocular PPE during an AGP goes against both PHE and WHO guidance, a choice that some NHS Hospital Trusts may not be willing to accept.

Most surgeons reported that their donned PPE allowed a full range of motion, dexterity and tactility despite all experiencing a degree of discomfort at some stage of the procedure. Although not subjected to an objective assessment, communication was reportedly problematic in all ten clinical evaluations. Although this attenuation in communication may have been improved by use of an FFP3 mask

rather than the utilised reusable half-face respirators, this may not be a feasible solution in times of extreme single-use PPE shortages. In an attempt to mitigate surgical error through miscommunication due to respirator use, simple sign language systems that can be used as adjuncts during otolaryngology procedures have been successfully introduced (Wilkinson et al., 2020) and have the potential to be introduced for otology procedures specifically. All half-face masks used in the clinical evaluations were compliant with European Standards for the technical specifications for respiratory PPE, hence there were no concerns over surgeons' vital physiological parameters.

7.5 CHAPTER SUMMARY

This chapter details the preclinical and clinical studies that facilitated the restart of CI and other mastoid surgery in NUH NHS Trust during the first wave of COVID-19. Cochlear implantation carried on through the subsequent peaks of the pandemic hence continued to minimise the period of auditory deprivation in pre-lingually deaf children. Although the ensemble of a FFP3 mask and safety spoggles proved the most effective PPE solution for CI and other mastoid surgery, access to disposable PPE resources was and still is at times extremely limited, hence reusable half-face mask are now utilised by most HCWs at NUH NHS Trust. There is no 'one-size-fits-all' PPE solution, yet NHS employers are obliged to maximise equality in access to PPE resources for all individuals, regardless of ethnic background and gender. The operating microscope makes the

use of ocular PPE in CI and other mastoid surgery challenging, however, there is clear national and international guidance recommending the use of ocular PPE during all AGPs. The experiments within this chapter have also shown that the use of a drape tent is an additional effective IPC measure and is therefore recommended to mitigate the spread of mastoid-drill induced contamination.

8. SUMMARY AND DISCUSSION

8.1 RESEARCH AIMS

The overall objective of this thesis was to examine the development of behavioural and cortical correlates of EF in NH children and children with CIs, with the subsequent aim of establishing whether such measures can explain individual variability in CI language outcome. To address this, NH children and paediatric CI users underwent fNIRS imaging whilst performing a behavioural EF task in experiments of both cross-sectional and longitudinal design. Unfortunately, an outbreak of the novel coronavirus (SARS-CoV-2) led to an international public health emergency that not only halted cochlear implantation procedures at auditory implant programmes throughout the UK, but also created a substantial pause in face-to-face research activity. However, a preclinical study and the subsequent implementation of recommendations on the PPE and IPC measures required for CI surgery during the COVID-19 pandemic, led to a restart of paediatric cochlear implantation at the NHS Hospital Trust that housed the research site for this thesis work. This not only minimised the period of auditory deprivation in deaf children awaiting CIs, but also facilitated subsequent participant recruitment to the experiments within this thesis. Furthermore, the parent-reported measures study enabled the investigation into the association between behavioural EF and language outcome to continue via non-participant facing methodology in both cohorts of children. Although the pause in face-to-face research activity

hampered achievement of some thesis goals, contingency plans substantially mitigated the effect that COVID-19 had upon this work.

The first aim of this thesis was to examine the development of behavioural EF in both NH children and paediatric CI users, and the second aim to investigate the relationship between behavioural EF and language performance in each cohort. Chapter four explored between-subject variability in EF performance (via behavioural EF tasks and parent-reported measures) in addition to the evolution of individual participants' performance on behavioural EF tasks over time and with increasing chronological age. Chapter five examined the association between measures of behavioural EF and language performance. Due to the small sample size of paediatric CI users it was impossible to assess individual variability in performance on behavioural EF tasks in this group of children specifically. However, the parent-reported measures experiment facilitated an evaluation of between-subject variability in behavioural EF, and furthermore, an assessment of the relationship between behavioural EF and language ability in both cohorts of children. The third aim of the thesis was to investigate behavioural EF-evoked cortical activation within prefrontal and superior temporal cortices of NH children and children with CIs, and whether this correlated with language ability. Unfortunately, the limited number of paediatric CI users recruited to the cross-sectional experiments prevented formal statistical analysis of the association between behavioural EF-evoked cortical activation

and language in this cohort of participants. However, the sample size for NH participants catered for such an analysis in this group of children.

The fourth aim of this thesis was to evaluate the suitability of fNIRS for acquiring repeated measures of behavioural EF task-evoked cortical activation and connectivity, in addition to repeated measures of resting-state connectivity, from the prefrontal and temporal brain regions of NH children and children with CIs. Following this fundamental step, the fifth aim was to examine how these cortical correlates evolved over time and following cochlear implantation. The final aim was to investigate whether these cortical correlates could predict later language outcome in both groups of children. All these aims were addressed in chapter six. However, it was not possible to evaluate the impact of cochlear implantation on the development of resting-state connectivity and connectivity on behavioural EF-evoked cortical activation due to the restricted sample size of paediatric CI users. The limited number of participants in this group also prevented an investigation into whether these cortical correlates could predict later CI language outcome. Nonetheless, this latter analysis was performed for the cohort of NH children.

The seventh, and final, results chapter of this thesis details the systematic-based evaluation of PPE and IPC measures that

facilitated the safe recommencement of CI surgery at NAIP within NUH NHS Trust during the COVID-19 pandemic.

8.2 SUMMARY OF FINDINGS

8.2.1 Main Findings of Chapter 4

1) A substantial level of between-subject variability in behavioural EF task performance was observed in NH children of an extremely similar chronological age. This finding relates to performance on various IC and WM tasks that were administered to children spanning the age range of eight months to six years. Unfortunately, it was not possible to examine variability in behavioural EF task performance amongst individual paediatric CI users due to the limited sample size of this group of participants.

2) The EF tasks employed in this thesis provided a measurement of the evolution of EF performance over time, with individual differences in the trajectory of performance observed amongst NH infants and children. Whilst the overall tendency was for EF performance to increase with age, performance was significantly associated with age in some EF tasks, but not others.

3) Parent-reported performance of behavioural EF also varied widely in similarly aged individuals within both the NH and CI

group. Interestingly, the only participants that exhibited clinically elevated BRIEF scores were paediatric CI users.

8.2.2 Main Findings of Chapter 5

1) Performance on behavioural EF tasks was not associated with language ability in preschool age (4 to 6 years old) NH children. However, parent-reported measures of global EF were found to significantly correlate with language performance in both NH children and paediatric CI users of preschool age. This association was significantly stronger in children with CIs compared with their NH peers.

2) There was no association between performance on behavioural EF tasks and parent-reported measures of EF in NH preschool-aged children.

3) Artefact-free cortical activations to behavioural EF tasks were successfully acquired bilaterally from ROIs overlying the prefrontal and superior temporal cortices of preschool-aged NH children and paediatric CI users.

4) A significant association between the amplitude of EF-evoked cortical activation overlying the left DLPFC and language performance was observed in NH participants of preschool age.

5) The amplitude of EF-evoked cortical activation within superior temporal regions of the paediatric CI participant was lower than that observed for NH peers, whilst the amplitude of activation within prefrontal regions was comparable between the two groups of preschool-aged children.

8.2.3 Main Findings of Chapter 6

1) Repeated measurements of resting-state connectivity and connectivity on EF task-evoked brain activation were successfully acquired from NH children and a paediatric CI user using fNIRS. Phase Transfer Entropy (PTE) connectivity analysis was specifically employed to analyse the paediatric fNIRS data, enabling the direction of any connectivity predictive of EF or language performance to be estimated.

2) Bottom-up, resting-state connectivity between ROIs overlying the right auditory and right prefrontal regions in NH infants and toddlers significantly predicted future language performance.

3) Both top-down and bottom-up connectivity on EF task-evoked brain activation between ROIs overlying left prefrontal and left superior temporal regions of NH toddlers significantly predicted future EF performance, which in turn was significantly associated with language performance.

4) The development of intra-hemispheric fronto-temporal connectivity appears to peak at 2 years of age in typically-developing children, indicating that connections between EF and language processing regions are potentially mature by the third year of life.

5) Connectivity data acquired from a CI participant both pre- and post-cochlear implantation suggested that left hemispheric fronto-temporal connectivity was weaker for this paediatric CI user compared with NH peers. However, top-down and bottom-up connectivity between left prefrontal and superior temporal regions was observed to increase in the months following CI device insertion.

8.2.4 Main Findings of Chapter 7

1) A preclinical, objective assessment of simulated CI surgery revealed mastoid drill-induced contamination extended further than reported in previous studies. This mixture of droplets, bone, blood and tissue spread into the typical position of the operating surgeon, scrub nurse and anaesthetist. Both preclinical and clinical evaluations showed the use of a drape tent to be an effective way of mitigating the spread of this mastoid drill-induced contamination.
2) The hypothesis that the SARS-CoV-2 virus is transmitted via aerosols has been subject to controversy. Nonetheless, mastoidectomy is widely accepted to be an AGP. At the time

of writing this thesis, PHE guidance was that all HCWs should don an FFP3 mask, or equivalent grade reusable respirator, in addition to adequate eye protection to minimise the transmission of COVID-19 during an AGP.

3) The challenge of combining of eye protection with the oculars of an operating microscope and impaired communication were drawbacks of PPE options. However, a systematic risk-based evaluation revealed that the ensemble of a half-face FFP3 mask and safety spoggles had superior performance across all aspects of the PPE assessment. This finding led to the development of recommendations on PPE and IPC measures required for CI surgery, the implementation of which enabled the restart of paediatric cochlear implantation at NAIP within NUH NHS Trust.

4) Clinical evaluations of the first ten CI surgeries during the pandemic revealed that all cases were performed safely. However, the ‘one-size-fits-all’ approach to PPE needs to be addressed to prevent the inadequate fitting of PPE, which tends to be particularly problematic for female and ethnic minority HCWs.

8.3 GENERAL DISCUSSION

8.3.1 The Association Between Measures of Behavioural Executive Function and Language Performance

The findings of Chapter 4 demonstrated that substantial variability in performance on behavioural EF tasks occurs amongst NH infants, toddlers and preschool-aged children. However, a lack of standardisation for the behavioural EF tasks employed in this thesis (Carlson, 2005) meant that it was impossible to ascertain whether a participant was exhibiting typical or atypical EF development relative to their chronological age. With respect to the EF tasks undertaken by infants and toddlers in the longitudinal fNIRS experiment, it was not possible to establish whether behavioural performance on the A-not-B, tongue and mommy/me tasks was predictive of future language performance due to the restrictions that COVID-19 placed on the methodology of this study. Behavioural performance on the Go/NoGo and N-back tasks undertaken by preschool-aged children was not associated with language ability, although caution must be exercised over this finding due to the associated restricted sample size. The BRIEF parent-reported measure is a standardised and validated rating scale for assessing behavioural EF. Parent-reported BRIEF scores were significantly associated with language performance in both NH and CI participants of preschool age. Since this tool indicates clinically elevated BRIEF scores, it seems logical to include it in the clinical workup of all children presenting with delayed language development. The findings of Chapter 5 highlight the importance of

a routine evaluation of behavioural EF performance in deaf children since a substantial number of paediatric CI users exhibited clinically elevated BRIEF scores. The BRIEF tool is only validated for use from 24 months of age upwards, hence is unable to assess behavioural EF in the first two years of life. However, behavioural measures of infant attention have already been shown to predict later EF (Cuevas & Bell, 2014) and language (Eggebrecht et al., 2017; Mundy et al., 2007) performance. Since clinically validated measures of joint attention such as the Early Social Communication Scales (Mundy et al., 2003) and the Communication and Symbolic Behavior Scales-Developmental Profile (Wetherby et al., 2002) are already available for use in early infancy, it is feasible that such tools could be implemented to gain measures of behavioural EF prior to the implementation of the BRIEF parent-reported rating scale.

Despite the attributes of the BRIEF tool and measurements of behavioural attention for identifying children at risk of executive dysfunction and deficient language development, these methods are associated with other limitations such as reporter bias and refusal of a participant to engage in an active behavioural task. Hence, the acquisition of objective measurements that require minimal participant co-operation (such as fNIRS correlates of resting-state connectivity) in addition to validated behavioural measures, may improve the accuracy of any evaluation aimed at identifying children at risk of deficient EF and subsequent atypical language

development. This would be particularly useful for paediatric CI recipients where costly rehabilitation resources could be directed to those most in need (Group U.C.I.S., 2004).

8.3.2 Suitability of fNIRS for Assessing Behavioural Executive Function-evoked Cortical Activation

The results of Chapter 5 provide confirmation of the suitability of fNIRS for measuring cortical responses to behavioural EF tasks in typically-developing preschool-aged children. Importantly however, the current study provides an original demonstration of the ability of fNIRS to detect behavioural EF-evoked cortical activation in paediatric CI users. Time-course analysis revealed that fNIRS recordings were unaffected by CI device generated artefacts that are known to adversely affect other neuroimaging techniques such as EEG (Bortfeld, 2019; Saliba et al., 2016). The current study adds to a relatively limited number of existing studies that demonstrate the feasibility of using fNIRS repeatedly with the same paediatric NH individuals (Moriguchi & Hiraki, 2011) and paediatric CI users (Wang et al., 2021). Furthermore, the number of paediatric participants that refused to wear the fNIRS equipment or became distressed throughout the fNIRS testing session was minimal in both the cross-sectional and longitudinal experiments. Although there was a substantial attrition rate amongst the CI participants, there was no evidence to indicate this was due to participant discomfort or intolerance for the fNIRS scanning procedure. In fact, subject withdrawal in this group of children was mainly attributed to the

circumstances surrounding COVID-19. In the paediatric CI users that co-operated with the fNIRS experiments, there were no adverse events or difficulty with optode placement over the newly implanted CI device.

It is interesting that behavioural performance on EF tasks was not associated with language outcome, yet the amplitude of behavioural EF task-evoked cortical activation measured with fNIRS did significantly correlate with language ability in NH children recruited to the cross-sectional experiment. Unfortunately, the COVID-19 pandemic scuppered an evaluation of whether such EF-evoked brain activation was related to language performance in paediatric CI users. Nonetheless, the current findings demonstrate that cortical correlates of behavioural EF have the potential to better inform healthcare professionals of an individual's executive functioning, which may be impacting on their language development. The aforementioned is currently applicable to NH children only, hence future studies involving children with CIs are required to examine whether the same or different fNIRS correlates of behavioural EF (i.e. activation of the left DLPFC) are associated with language performance in paediatric CI users. Since this thesis has also revealed that parent-reported measures of behavioural EF are significantly associated with language outcome in preschool-aged NH and deaf-implanted children, it could be argued that it is more efficient to employ validated tools such as the BRIEF to examine for executive dysfunction. However, as discussed in the following

sections, there are limitations associated with both parent-reported measures and fNIRS imaging. Thus, having both subjective and objective measures of behavioural EF may improve the sensitivity of any clinical assessment performed for NH and deaf-implanted children who are not reaching language milestones. Whilst examining the clinical applicability of fNIRS was not the aim of the current research, the results of Chapter 5 do suggest that fNIRS was able to detect individual differences in behavioural EF-evoked cortical activation. However, at present, fNIRS data is only ever formally interpreted and analysed at the group-level. Furthermore, the current experiments have highlighted that the suitability of fNIRS as a clinical tool for examining cortical correlates of behavioural EF is associated with practical constraints that limit its use at the individual level. Such drawbacks included: 1) inadequate levels of light intensity being transmitted and received between source-detector pairs, likely due to the attenuation by dark or thick hair, causing the exclusion of some fNIRS recordings, and; 2) refusal to wear the fNIRS head cap. Nonetheless, future advances in fNIRS data analysis methods in addition to the use of hair-penetrating brush optodes (Khan et al., 2012) and/or optodes with a small footprint (Pollonini et al., 2016), may resolve these limitations.

8.3.3 Predicting Language Outcome from Resting-state Cortical Connectivity and Connectivity on Behavioural EF Task-evoked Brain Activation

The findings of Chapter 6 demonstrated that correlates of resting-state fronto-temporal connectivity in NH infants and toddlers significantly predicted future language outcome. Evidence from established EEG studies demonstrates that infant fronto-temporal connectivity is associated with joint attention (Eggebrecht et al., 2017), and that both these measures predict later language development (Mundy et al., 2003). Since behavioural attention is reportedly fundamental to EF development (Garon et al., 2008), it is feasible that the fNIRS correlates of resting-state fronto-temporal connectivity acquired in the current longitudinal experiment were a neural marker of attention, that was subsequently predictive of language performance. The finding that bottom-up connectivity between right auditory and right BA 10 ROIs was the specific correlate predictive of language outcome in the current longitudinal experiment is pertinent since established evidence reports that right BA 10 activation reflects attention to auditory processing (Medalla & Barbas, 2014; White & Langdon, 2021). This hypothesis aligns with that made in Chapter 5, whereby the behavioural EF task-evoked activation observed in the left DLPFC of preschool-aged NH children was suggested to reflect recruitment of the central executive and the subsequent ability of a participant to dedicate greater attention to listening tasks and language acquisition. Although resting-state fronto-temporal connectivity was not predictive of future

behavioural EF in the current longitudinal experiment, this was the case in an EEG study that recruited a substantially larger number of participants (Broomell et al., 2019). Since the rate of receptive and expressive language acquisition is greatest between 18 months and 5 years of age (O'Muircheartaigh et al., 2013), it is important to identify and manage children at risk of language delay as early in life as possible. In the current longitudinal experiment, the youngest participant from whom resting-state connectivity data were acquired was aged 8 months, however resting-state fNIRS imaging has already been successfully performed in younger infants and neonates (Hu et al., 2020). Therefore, from a methodological perspective, fNIRS offers a safe and non-invasive tool for studying resting-state connectivity in young infants that can subsequently predict future language performance. However, caution should be exercised in drawing firm conclusions as the current study provides the first known examination of the prognostic value of fNIRS brain imaging in terms of EF and language outcome. Future work should aim to validate these findings in a larger sample of NH infants and toddlers. Furthermore, the experiments within this thesis were unable to examine the relationship between fNIRS correlates of resting-state connectivity and language performance in children with CIs, hence future research is required to establish whether such measures can predict language outcome in paediatric CI users. Investigations into the relationship between fNIRS correlates of resting-state connectivity and behavioural measures of attention in both NH and deaf-implanted children would also be informative.

Chapter 6 also revealed that fNIRS correlates of fronto-temporal connectivity on tongue task-evoked cortical activation in NH toddlers were predictive of future behavioural EF, that was in turn significantly associated with parent-reported measures of language performance. Interestingly, behavioural performance on the tongue task was not predictive of future EF in terms of BRIEF score. Although fNIRS correlates of resting-state fronto-temporal connectivity can be acquired at an earlier stage in development than correlates of connectivity of tongue-task evoked brain activation, the tongue task is suitable for children as young as 24 months, hence the cortical correlates of this task also have potential to predict behavioural EF within the critical period of language acquisition (O'Muircheartaigh et al., 2013). Furthermore, observations from the longitudinal study revealed that some toddlers were more engaged in the tongue task than the resting-state task, possibly due to the reward involved. Although future studies involving larger numbers of NH participants are required to validate these preliminary findings, fNIRS correlates of fronto-temporal connectivity on tongue task-evoked cortical activation show promise for identifying toddlers at risk of less favourable EF, who may subsequently benefit from appropriate rehabilitation. Future work should also look to determine whether such correlates of connectivity are also predictive of executive dysfunction in deaf-implanted children, where intervention aimed at improving EF and language outcome may reap its greatest reward.

8.4 LIMITATIONS

8.4.1 Sample of Normal-Hearing Children and Paediatric Cochlear Implant Users

As reiterated throughout this thesis, the change in the outcome measure use to assess language (that occurred part way through the experiments) restricted analyses of the association between behavioural and cortical correlates of EF and language performance in NH children. Specifically, in Chapter 5, data for less than 15 NH participants were included in the bivariate correlation analyses that examined the relationship between behavioural EF-evoked cortical activation and language outcome. Furthermore, in Chapter 6, data for only eight NH participants were included in the regression analyses that examined the ability of resting-state connectivity to predict future language outcome. Although the significantly positive association between behavioural EF-evoked cortical activation within the left DLPFC and language outcome is a novel finding in NH children, the ability of right-hemispheric connectivity to predict later language outcome aligns with existing evidence (Mundy et al., 2003). Nonetheless, further studies to validate these findings are required before any definitive conclusions can be made. Such studies should ideally account for factors other than EF that are known to be associated with language outcome such as socioeconomic status, family history of language or vocabulary difficulties and parental education (McKean et al., 2017), since these were not considered in the current experiments. The revelation that connectivity on EF-evoked brain activation was

predictive of later BRIEF scores in NH children can be interpreted with greater confidence due to the larger sample size associated with the corresponding regression analysis.

The very limited number of participants recruited to both the cross-sectional and longitudinal fNIRS experiments prevented an examination of the relationship between measures of EF and language in paediatric CI users. However, the parent-reported measures experiment confirmed the significant association between these measures that has been reported in a plethora of other studies (Beer et al., 2014; Kronenberger, Beer, et al., 2014; Kronenberger et al., 2018; Kronenberger et al., 2020; Pichora-Fuller et al., 2016; Rönnberg et al., 2008) and further fuels the theory that behavioural EF contributes to the variability in CI language outcome.

8.4.2 Experimental Design

A cross-sectional approach was taken in the parent-reported measures experiment and one of the fNIRS experiments, which aimed to assess the association between behavioural measures of EF and language ability and EF-evoked cortical activation and language performance respectively. However, the correlational approach taken in these experiments does not allow causation to be inferred. Specifically, whilst the longitudinal experiment confirmed that fronto-temporal connectivity on EF task-evoked brain activation was predictive of later behavioural EF performance, it was not

directly predictive of language ability. Throughout this thesis it is suggested that fNIRS correlates of fronto-temporal connectivity may be used to gain information about future language ability. This suggestion is based on the finding that significant fronto-temporal connectivity on EF task-evoked brain activation was predictive of BRIEF scores, that were turn associated with CCC-2 scores on bivariate correlation analysis. However, as discussed in section 8.4.3, confounding factors may contribute to the significant association between these parent-reported measures of EF and language. Nevertheless, the observational longitudinal approach did detect that fNIRS correlates of resting-state connectivity were directly predictive of future language performance, hence supporting the hypothesis that fronto-temporal connectivity has a causal role in language development and processing.

8.4.3 Measures of Behavioural Executive Function and Language Performance

Prior to COVID-19, it was planned for all participants recruited to the cross-sectional and longitudinal fNIRS experiments to undergo a PLS-5^{UK} assessment with a qualified Speech and Language Therapist. However, the inability to continue with face-to-face language assessments meant that age-appropriate parent-reported measures replaced the PLS-5^{UK} part way through this thesis work. As the specific measure used to assess language outcome varied amongst participants, the statistical analyses that were performed to examine the association between fNIRS cortical correlates and

language outcome in NH children were associated with limited sample sizes. Furthermore, these analyses were exploratory in nature and it must be appreciated that the observed significant association between cortical correlates of EF and language in NH children may have arisen simply due to chance. Thus, an element of caution should be exercised over the conclusions of these analyses.

In the cross-sectional experiment, behavioural IC and WM-evoked cortical activation in NH children was significantly associated with performance on the PLS-5^{UK}, but not the CCC-2 parent-reported measure. Although these two assessments evaluate many of the same elements of language such as semantics, syntax, nonverbal communication and social interaction, they also assess different elements. For example, the PLS-5^{UK} additionally evaluates literacy skills, whereas the CCC-2 examines pragmatic language impairments. The differences amongst these two assessments may partly account the finding that only PLS-5^{UK} scores were significantly correlated with behavioural EF-evoked cortical activation. Another potential contributing factor to this finding is reporter bias associated with parent-reported measures. Conversely, it could be argued that an evaluation of a child's language skills by a parent/guardian who observes the child daily, provides a more accurate reflection of their language ability than a one-off clinical assessment by a healthcare professional.

Interestingly, in the longitudinal experiment, resting-state fronto-temporal connectivity in infants and toddlers was significantly predictive of future performance on the CCC-2 measure. Unfortunately, PLS-5^{UK} scores were not available for the longitudinal participants, so it was impossible to ascertain whether resting-state connectivity was able to predict language outcome measured via this assessment. Connectivity on EF task-evoked activation in toddlers was not directly predictive of CCC-2 scores, yet this cortical correlate was found to predict future BRIEF scores, which were in turn significantly associated with CCC-2 scores in the separate cross-sectional parent-reported measures experiment (involving preschool-aged children). Again, it would have been informative to have PLS-5^{UK} data available for the regression analyses that examined the ability of connectivity on EF task-evoked activation to predict later language outcome. Since performance on the PLS-5^{UK} and CCC-2 were associated with cortical correlates of behavioural EF and resting-state connectivity respectively, it seems appropriate to employ both a clinical assessment and a parent-reported measure of language ability in future research studies designed to examine the relationship between EF and language outcome in both NH and deaf-implanted infants and children.

The larger sample sizes associated with the parent-reported measures experiment deliver confidence to the finding of a significant association between behavioural measures of EF and language performance in both NH and children with CIs. This cross-

sectional experiment employed the BRIEF and CCC-2 measures. As described earlier, one aim of the CCC-2 is to identify pragmatic language impairment, which is a feature of ASD. Executive dysfunction, which is screened for in the BRIEF measure, is also typical of ASD. Hence, both the BRIEF and CCC-2 measures enquire about characteristics of ASD, which may partly explain the significant association between CCC-2 and BRIEF scores. However, the General Communication Composite (GCC) within the CCC-2 was the specific score used in the statistical analyses for this experiment. This score concentrates on aspects of pragmatic language impairment rather than other behaviours typical of executive dysfunction/ASD, which are specifically examined in the BRIEF measure. Furthermore, pragmatic language impairment is not unique to ASD and may be found in other groups of children such as those with learning disabilities, specific language impairment and traumatic brain injuries (Ptok, 2005). The social Interaction Deviance Composite (SIDC) is an additional component within the CCC-2 that aims to identify communication styles indicative of ASD. It is interesting that within the parent-reported measures experiment, only two out of the seventeen paediatric CI recipients that had elevated BRIEF scores had a CCC-2 profile suggestive of ASD. None of the NH children with elevated BRIEF scores had a communicative profile indicative of ASD. Thus, most children with elevated BRIEF scores did not have a communicative profile suggestive of ASD.

8.4.4 Measurement of Behavioural Executive Function-evoked Brain Activation and Cortical Connectivity

A substantial limitation of fNIRS is the lack of ability to image the underlying anatomy of the brain, signifying that anatomical variation amongst individual participants was not accounted for in the current experiments. In the present experiments, the optode array was placed in relation to anatomical surface landmarks, with the mean position of each optode (at the participant group-level) from such landmarks used for cross-referencing with the international 10-20 system and corresponding Brodmann areas. For these reasons, it is likely that variability existed across subjects in the precise origin of cortical responses. Furthermore, due to the 3cm distance between source and detector optodes within the measurement array, in addition to the limited spatial resolution of fNIRS (Lloyd-Fox et al., 2010), it was impossible to determine the exact origin of cortical activations. Therefore, whilst activation and connectivity are referred to as occurring within and between ROIs measured to overlay specific prefrontal and superior temporal regions, it is possible that these haemodynamic changes were occurring in neighbouring cortical areas.

Whilst more accurate estimation of the anatomical origin of cortical activations is possible via the use of 3D digitisers and spatial-registration software (Singh et al., 2005; Tsuzuki et al., 2012), the Hitachi ETG-4000's magnetic 3D Probe Positioning Unit was not used in the current experiments. This is because previous in-house

pilot studies revealed that measurements were difficult to acquire, likely due to the metal doors of the sound booth being in close vicinity of the magnetic receiver and transmitter unit. It was anticipated that the aforementioned may exacerbate any restless and fidgety behaviour amongst some infant and younger participants and subsequently prevent the acquisition of good quality experimental fNIRS data. Given that paediatric CI users undergo MRI imaging prior to cochlear implantation, it is feasible that patients' own structural images could be used for spatial co-registration of fNIRS data. Encouragingly, this has already been performed for a typically-developing infant who underwent both fMRI and fNIRS imaging (Bulgarelli et al., 2018).

High-density diffuse optical tomography (HD-DOT) is an optical neuroimaging modality that, like fNIRS, uses near-infrared light to measure the haemodynamic response. However, unlike standard fNIRS equipment, HD-DOT uses a dense source-detector array with multiple separations which enables optimised lateral resolution and depth profiling. Studies have already demonstrated the spatial resolution associated with this technique to approach that of fMRI imaging (Eggebrecht et al., 2014; Eggebrecht et al., 2012). This evidence has fuelled the development of specific high-density fNIRS systems, which also employ multi-distance source-detector separations, and are at present leading to an ever increasing overall accuracy of fNIRS imaging (Shin et al., 2017). Despite these advances, the techniques of HD-DOT and high-density fNIRS

imaging remain limited to imaging the superficial cortex and hence, cannot access deep subcortical structures. This highlights another limitation of employing fNIRS imaging in the evaluation of behavioural EF-evoked cortical activation, since subcortical structures including the striatum and thalamus have also been implicated in EF processing (Alcauter et al., 2014; Ullman et al., 2014). Furthermore, although the focus of this thesis work was to examine prefrontal and superior temporal brain regions, the parietal cortices have also been shown to exhibit increased activation during paediatric EF tasks (Bunge et al., 2002; Crone et al., 2006; Durston et al., 2006). Connectivity between frontal and parietal cortices has also been implicated in early EF development (Alcauter et al., 2014; Buss et al., 2014; Buss & Spencer, 2018; Mehnert et al., 2013). In the current experiments, parietal areas were not examined due to the limited coverage of the optode array. However, numerous existing fNIRS studies have successfully measured fNIRS responses within the bilateral parietal cortex of typically-developing children via the employment of appropriate measurement arrays (Buss et al., 2014; Mehnert et al., 2013). Thus, it would be beneficial for any future work examining the association between cortical correlates of EF and language outcome to include measures of parietal fronto-temporoparietal activation and connectivity.

Another drawback for employing fNIRS imaging to examine the cortical correlates of behavioural EF relates to the temporal resolution associated with this technique (Lloyd-Fox et al., 2010;

Toronov et al., 2007). As the temporal resolution associated with this technique is inferior to that exhibited by other neuroimaging techniques such as EEG, it was not possible analyse and use the data acquired during the A-not-B and mommy/me tasks in the manner that was originally planned due to the short duration of the trials within this task. Furthermore, caution must be exercised when interpreting the findings that relate to fronto-temporal connectivity within this thesis as estimates of directed effective (PTE) connectivity rather than functional connectivity were employed. Where comparisons have been made between the findings of the current experiments and established evidence, it must be appreciated that the majority of studies that have examined cortical connectivity and its role in EF processes, have employed functional connectivity analysis methods (Fiske & Holmboe, 2019). Nevertheless, the use of PTE connectivity analysis has been successfully implemented and established in many neuroimaging techniques, including fNIRS (Urquhart et al., 2020; Wang & Chen, 2020) and EEG (Ahmadi et al., 2020; Lobier et al., 2014; Yang et al., 2013). However, it must be acknowledged that PTE connectivity values are merely estimates of connectivity since they detail the causal direction of information of flow based on conditional probabilities (Ursino et al., 2020).

8.5 DIRECTIONS FOR FUTURE RESEARCH

8.5.1 Clinical Interventions to Improve Executive Function

The findings throughout this thesis align with the current literature which states that behavioural EF and language are bidirectionally and reciprocally related. Hence, clinical interventions aimed at improving EF are expected to support language development. Evidence from numerous studies indicates that cognitive training interventions can effectively promote executive functioning in otherwise healthy children. Such training programmes have been demonstrated to improve WM (Jaeggi et al., 2011), IC (Thorell et al., 2009) and CF (Karbach & Kray, 2009) skills in children from a young age. Specifically, available interventions include: 1) computer-based training programs such as Cogmed Working Memory Training (CWMT) (Holmes et al., 2015; Klingberg, 2010) and N-back Working Memory Training (NBWMT) (Jaeggi et al., 2011); 2) academic-based courses that teach EF skills in the school environment (Blair & Raver, 2014), and; 3) parent- and family-administered methods within the home setting (Verkerk et al., 2012). However, the majority of studies that have analysed cognitive training have been conducted in older children, with only a small number having targeted preschool-aged children (Rueda et al., 2012; Thorell et al., 2009) and infants (Wass et al., 2008). The interventions used in published studies to date are all unsuitable for use in infants due to the underdevelopment of fine motor and other skills required for task engagement. A potential solution to this problem has been provided by Wass et al. (2011) who used eye

gaze-contingent paradigms to train typically-developing 11 month old infants on a battery of attentional control tasks. Post-training assessments revealed improvements in cognitive control and sustained attention, with the amount of training correlating with the degree of improvement on some measures (Wass et al., 2011). Given that infant visual and joint attention has been shown to predict later EF and language performance (Cuevas & Bell, 2014; Holmboe et al., 2008), training attentional control may be a strong target for early clinical intervention. Since the findings in Chapter 6 not only support existing evidence that fronto-temporal connectivity is associated with attention processes (Eggebrecht et al., 2017), but also that this connectivity reaches its maximum peak at about 24 months (Bulgarelli et al., 2020), it seems appropriate to implement such training programmes as early as possible in order to support the development of adequate neuronal connections that are fundamental to behavioural EF. Future work should aim to validate the effectiveness of infant cognitive training programmes such as that introduced by Wass et al. (2011).

With respect to EF intervention in CI recipients, it is already common for speech and language rehabilitation packages to incorporate practice with EF skills such as controlled attention, IC and cognitive efficiency (McConkey Robbins, 2009). Although a study has shown that the computer-based training programmes CWMT and NBWMT are able to improve the WM performance of paediatric CI users aged between 7 and 15 years (Kronenberger et

al., 2011), the findings of a meta-analysis cast doubt on the clinical relevance of such WM training programs in terms of their ability to improve every day EF behaviours (Melby-Lervåg & Hulme, 2013). Further research is required to examine whether behavioural attention and cortical connectivity can predict future EF and language outcome in deaf infants and toddlers. Should this be the case, early implementation of EF rehabilitation (such as attentional control training) aimed to coincide with the auditory sensitive period within the first three and a half years of a child's life (Sharma et al., 2005; Sharma et al., 2007), has the potential to maximise both EF and language outcome. During this sensitive period of auditory development, the central auditory system is particularly plastic (Lazard et al., 2012; Sharma et al., 2005), hence connections with higher-order prefrontal brain regions that are fundamental to behavioural EF are likely being established and pruned (Kral, 2013; Kral et al., 2019; Kral et al., 2016). Since sensory deprivation delays cortical synaptogenesis (Kral & O'Donoghue, 2010; Kral & Sharma, 2012), auditory rehabilitation with cochlear implantation during the auditory sensitive period would also be expected to maximise EF outcome via facilitating the development of fronto-temporoparietal connectivity. However, further work is required to investigate this hypothesis since limited recruitment of CI participants to the current experiments prevented such an examination here. Nonetheless, the findings of this thesis suggest that fNIRS is an adept tool for future investigations into fronto-

temporoparietal connectivity in paediatric CI recipients, and how such connections change over time and with cochlear implantation.

8.5.2 Understanding Cortical Correlates of Behavioural Executive Function in Paediatric Cochlear Implant Users

The ability to process auditory speech information relies upon a wide-spread fronto-temporoparietal cortical network that can be divided into ventral and dorsal pathways (Hickok, 2012; Hickok & Poeppel, 2007). As discussed in Chapter 6, regions within this hierarchical network that are in close proximity to the auditory cortex are involved in processes such as phonological word form detection, whereas those within frontal areas are involved in higher-level processes that facilitate the analysis of semantic and syntactic relations (Friederici, 2011; Skeide & Friederici, 2016; White & Langdon, 2021). However, listening under adverse conditions has been shown to modulate input from the prefrontal cortex, meaning that top-down executive processes regulate listening effort (Du et al., 2016; Mattys et al., 2009; Peelle, 2018). In a recent fNIRS study performed in adults, a distinct pattern of activation within frontal and left temporo-parietal brain regions was observed whilst listeners were exposed to increasingly adverse listening conditions (White & Langdon, 2021). The least challenging conditions (which required the processing of undegraded syntactic structures) were found to recruit the left inferior frontal gyrus (LIFG), whereas increasingly difficult conditions (simulating CI listening) were observed to sequentially activate the left inferior parietal lobe (IPL)

and ultimately the left DLPFC and right BA 10 regions (White & Langdon, 2021). Since both the left IPL and left DLPFC areas are implicated in verbal WM processing (Baddeley, 2003) and the right BA 10 region in auditory attention processing (Medalla & Barbas, 2014), these findings suggest that difficult listening conditions are particularly reliant on higher-order attention and verbal WM mechanisms. Future work aimed at establishing whether EF-evoked cortical activation within the left DLPFC of deaf children is significantly associated with language outcome, as was observed for NH children in Chapter 5, would be incredibly informative. Furthermore, investigations into the relationship between right BA 10 activation and language performance in paediatric CI users would be prudent, especially since resting-state connectivity between right auditory areas and right BA 10 was significantly predictive of language outcome for NH infants and toddlers as described in Chapter 6. Interestingly, there is already evidence to suggest that recruitment of the left DLPFC may be predictive of future language performance in paediatric CI recipients. A PET study which examined resting-state cortical activity in severe-to-profoundly deaf children (aged 1 to 11 years) prior to cochlear implantation demonstrated that individuals with good speech understanding three years post-implantation exhibited enhanced metabolic activity in the left DLPFC compared with those who had poor speech perception (Lee et al., 2007). As discussed in Section 8.5.1, further research is required to establish whether correlates of cortical connectivity are predictive of future EF and language ability

in deaf children. It could be hypothesised that correlates of fronto-temporoparietal connectivity are more strongly associated with future EF and language outcome in paediatric CI users than NH children since effortful listening (that is typical for listening to the degraded input from a CI device) is more reliant upon attention and verbal WM processes, that in turn appear dependent on connections between the left superior temporal cortex, left IPL and left DLPFC. This theory is strongly supported by established evidence which demonstrates that behavioural verbal WM skills are significantly predictive of future language development in paediatric CI users, but not NH children (Kronenberger et al., 2020).

8.5.3 Future Development of Inclusive Personal Protective Equipment

Although over 40 million people had received two doses of the COVID-19 vaccine at the time of writing this thesis (GOV.UK, 2021), HCWs are continually expected to take precautions to minimise viral transmission of the SARS-CoV-2 virus. Since current COVID-19 vaccines aim to mount an IgG response and prevent viremia, they typically provide limited protection against viral replication within the airway which requires a local mucosal IgA response (Bleier et al., 2021). Hence, asymptomatic vaccinated individuals may still become infected with COVID-19 and transmit live virus from the airway (Bleier et al., 2021). As demonstrated in Chapter 7, inadequate fitting of PPE remains problematic for some HCWs, particularly females and ethnic minority individuals. The UK Health

and Safety Executive (HSE) has produced guidance on fit testing and advises which fit test method is applicable for each type of respiratory PPE (Health And Safety Executive [HSE], 2019). NHS employers are encouraged to adhere to such guidance to maximise adequate fit and protection for individual PPE wearers. Innovations such as the 'PPE Helper Programme' designed by a London hospital group have successfully provided PPE support, advice and education to HCWs and helped to counteract suboptimal PPE practice (Castro-Sánchez et al., 2021). The implementation of such behavioural interventions may have a considerable effect on the frequency and/or correctness of respiratory PPE use in the clinical setting (Luong Thanh et al., 2016). Furthermore, international organisations such as 'Women in Global Health' are in the process of collecting valuable survey data from women with the aim of improving PPE for female health workers (Women in Global Health' [WGH], 2021).

However, the main challenge for CI surgery is the combination of eye protection with the oculars of an operating microscope. Although Chapter 7 demonstrated that safety spoggles are a safe option, inadequate fit may be a hindrance for individual surgeons. Three-dimensional printing is a rapidly advancing field and the production of custom fit eyewear, with ensured compatibility with the operating microscope, may be possible with future developments in 3D printing technology (Huang & Zhang, 2014). The technique of 3D printing has also been used to develop frames

for filtering face piece respirators that have the potential to improve fit for individuals who cannot fit existing masks (McAvoy et al., 2021). If 3D printing of ocular and/or respiratory PPE is introduced into routine clinical practice, it is pertinent that all equipment is compliant with international standards and UK HSE guidance (Health And Safety Executive [HSE], 2020).

8.6 CONCLUSIONS

Executive function skills vary substantially amongst NH and deaf-implanted children. Behavioural EF performance and language ability are significantly associated in both cohorts, however the relationship is stronger in paediatric CI users than typically-developing individuals. This is most likely explained by top-down processes, such auditory attention and verbal WM mechanisms, regulating listening during adverse conditions such as listening through a CI device. Cortical activation elicited by EF behaviours may offer important information about the attention and effort that an individual dedicates to language acquisition, and thus help explain the variability in language outcome observed amongst children with and without CIs. Furthermore, cortical correlates of bottom-up and top-down fronto-temporal connectivity in NH infants and toddlers have the potential to predict future EF and language and identify those who would benefit from early intervention. Future research should look to determine if such cortical predictors can be extended to deaf-implanted children, in addition to whether attentional control-based training interventions are effective in

improving language outcome for paediatric CI recipients. The results reported throughout this thesis suggest that fNIRS is an adept tool for the repeated imaging of behavioural EF-evoked brain activation and cortical connectivity in children with and without CIs, bearing promise for its growing application in paediatric CI users.

9. APPENDICES

9.1 APPENDIX A: Long term ergonomic PPE questionnaire for otology surgeon participants

1. How long do you feel it is possible to wear the full-face snorkel and the full-face respirator mask for before each of them becomes uncomfortable?

2. Do you feel both the full-face snorkel and the full-face respirator mask are feasible PPE solutions that could potentially be worn during cochlear implant surgery?

3. If the full-face snorkel mask (like the full-face respirator mask) had regulatory approval, what PPE (out of all available PPE options) would you choose to perform a cochlear implantation on an individual with unknown COVID-19 status?

4. What issues might prevent you from using each of the full-face snorkel and the full-face respirator masks as PPE solution during cochlear implant surgery?

5. What do you think the implications of both the full-face snorkel and the full-face respirator mask will be on surgical training?

6. Did you pass or fail your FFP3 fit test?

7. If certified as PPE, would you consider using the full-face snorkel mask during cochlear implant surgery?

8. Would you consider using the full-face respirator mask during cochlear implant surgery?

9. Would you be comfortable doing cochlear implant surgery using a standard FFP3 mask and a face shield?

9.2 APPENDIX B: Clinical Evaluation of Recommended Personal Protective Equipment

Parameter being assessed for PPE/IPC	Please circle 'Yes' or 'No' as appropriate and give extra details if required.
Donning, doffing and changing of PPE	
Donning	Did you experience any difficulty donning the PPE according to NUH guidelines/instructions? (Yes/No) *If yes, please give details.*
Doffing	Did you experience any difficulty doffing the PPE according to NUH guidelines/instructions? (Yes/No) *If yes, please give details.*
Changing	Were you able to remove, change or replace pieces of PPE without contaminating other pieces of PPE in the ensemble and without doffing completely? (Yes/No) If not required, do you think it would have been possible to do all of the above? (Yes/No). *If no to any of the above, please give details.*
Usability of PPE	
Size	Was the PPE adequately sized? (Yes/No) If not adequately sized, did this limit your ability to perform CI surgery in any way? (Yes/No) *If performance was limited, please give details.*
Mobility, dexterity and tactility	Did the PPE allow the full range of motion, dexterity and tactility required to perform CI surgery? (Yes/No) *If no to any of the above, please give details.*

Vision	Did the PPE distort or limit your view of the surgical field in anyway? (Yes/No) *If yes, please give details.*
Communication	Were you able to effectively communicate with the scrub nurse and other members of the operating theatre staff? (Yes/No) *If no, please give details.*
Comfort	How long did you wear the PPE for in total? Did you experience any discomfort or anxiety during the surgical procedure? (Yes/No) *If yes, please give details, including the time onset of the discomfort/anxiety.*
Fit for purpose – PPE	
Sterility	In your opinion, did the PPE remain sterile throughout the procedure? (Yes/No) *If no, please give details.*
Level of protection	Have you passed a qualitative fit test for the FFP3 mask/half-face respirator worn during the procedure? (Yes/No) *If no, please give details.*
Junctions in the ensemble	Were any gaps identified between pieces of PPE? (Yes/No) If yes, were they closed with the use of tape or adjustments? (Yes/No) If yes, were there any other alternative pieces of PPE available that would have eliminated those identified junctions? (Yes/No). If yes, why were these not used? *Please give details.*

IPC drape 'tent'	
Assembly	Was the drape 'tent' assembled according to ENT UK guidelines (12) whilst maintaining sterility of the surgical field? (Yes/No) *If no, please give details.*
Disassembly	Was the drape 'tent' disassembled according to ENT UK guidelines (12)? *If no, please give details.*
Changing	Do you think you would have been able to easily change the drape 'tent' if it became contaminated during the procedure? (Yes/No) *If no, please give details.*
Mobility, dexterity and tactility	Did the drape 'tent' affect your mobility, dexterity or tactility during the procedure? (Yes/No) *If yes, please give details.*
View of the surgical field	Did the drape 'tent' affect your view of the surgical field during the procedure? (Yes/No) *If yes, please give details.*
Sterility	In your opinion, was sterility of the drape 'tent' maintained throughout the surgical procedure? (Yes/No) *If no, please give details.*

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