

Resting-state EEG in adults with Down syndrome

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Declaration

I, Sarah Hamburg, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

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Date:

Abstract

Individuals with Down syndrome (DS) show a high degree of inter-subject variability in cognitive ability. Elucidating factors associated with variability in cognitive function can inform us about intellectual disability severity and potentially provide biomarkers of ability for clinical trials targeting cognition in individuals with DS (including trials aimed at preventing cognitive decline).

Resting-state electroencephalography (EEG) can be used to obtain information about neural factors that may be underlying variability in cognitive function. This thesis uses eyes-open (EO; n=48) and eyes-closed (EC; n=36) resting-state EEG paradigms in adults with DS free from detectable signs of cognitive decline or dementia to identify EEG measures associated with general cognitive ability, and to investigate age-related changes in EEG activity in this population. Oscillations of interest were then modelled using dynamic causal modelling (DCM) to identify potential neurophysiological mechanisms underlying individual differences in general cognitive ability.

Initial analysis suggested that individuals with DS have an overall slower EC EEG spectrum (and particularly strong differences in alpha activity) compared to typically-developing age-matched control subjects (open source control dataset used). Within individuals with DS, increasing age was associated with EEG changes in both paradigms. When controlling for age, higher general cognitive ability was associated with higher delta power (EO only), higher theta power (EC only), and higher alpha peak amplitude (EC only). Modelling the theta-alpha network identified “intrinsic self-inhibition” as the most important neurophysiological parameter underlying the relationship between theta-alpha activity and general cognitive ability in this sample. Further analysis revealed a strong inverse relationship between occipital intrinsic self-inhibition and general cognitive ability.

Findings of this thesis enhance our understanding of neural factors associated with individual differences in general cognitive ability in adults with DS, provide a potential biomarker of ability for clinical trials, and indicate potential targets for cognitive enhancement in this population. The finding that increased inhibition may be associated with cognitive impairment in this population is in keeping with animal model literature and warrants further investigation.

Thesis overview

Chapter 1 provides an overview of Down syndrome (DS), including information about cognition and approaches to cognitive testing in this population. A review of resting-state EEG studies in adults with DS is provided by Chapter 2. Previous studies investigating the association between resting-state EEG measures and cognitive ability in adults with DS are limited, and are often confounded by the inclusion or potential inclusion of individuals with cognitive decline and dementia. All general methodology for the thesis is detailed in Chapter 3.

Chapter 4 investigates the feasibility of obtaining EO and EC resting-state EEG data in this population and also explores the extent to which findings from the participating sample are generalisable. The findings of Chapter 4 suggest that, when compared to a larger DS sample, the sample of participants in this thesis is slightly biased towards individuals with higher general cognitive ability, and this is further exacerbated for individuals able to complete both recording paradigms. Suggestions are provided to reduce potential sources of bias in future EEG studies involving adults with DS.

Chapter 5 compares EC resting-state EEG measures between individuals with DS and a group of chronologically age-matched and sex-matched typically developing (TD) controls (using an open source TD dataset). Findings suggest that individuals with DS have an overall slower EEG spectrum compared to matched TD control subjects (delta and theta power values are significantly higher, whereas alpha and beta power values are significantly lower), and higher variability for all EEG measures. Alpha activity shows particularly strong group differences.

Individual differences in EO and EC EEG measures (in both occipital and frontal regions), and their relationships with individual differences in general cognitive ability and age, were explored in Chapter 6. Overall, in the EO paradigm, increasing age was associated with increased alpha activity (power and alpha peak amplitude), and increased beta power. In the EC paradigm increasing age was associated with increased alpha peak amplitude and reduced delta power. When controlling for effects of age, higher general cognitive ability was associated with higher frontal delta power in EO recordings, and higher frontal theta power and frontal and occipital alpha peak amplitude in EC recordings.

The cortical network generating theta-alpha oscillations (i.e. extended alpha; 4-13 Hz) was modelled in Chapter 7 using dynamic causal modelling (DCM). The

neurophysiological parameter of intrinsic self-inhibition was identified as the most important parameter in this network underlying the relationship between theta-alpha activity and general cognitive ability. Further analysis revealed a strong negative relationship between intrinsic self-inhibition and general cognitive ability in the occipital region. Results suggest that a shift in excitation/inhibition (E/I) balance towards increased inhibition may be associated with greater cognitive impairment in DS. This finding is in accordance with recent mouse model work indicating the possible presence of over-inhibition in DS; however results presented here also suggest this general hypothesis may be over-simplified.

An overall discussion of the thesis is provided in Chapter 8. Together results indicate that exploring and potentially targeting mechanisms underlying EEG measures associated with individual differences in general cognitive ability in DS, instead of focusing on differences between individuals with DS and TD controls, may be a worthwhile strategy for cognitive enhancement in DS. In this thesis intrinsic self-inhibition was identified as a potential neurophysiological factor underlying individual differences in general cognitive ability. Further investigation of intrinsic self-inhibition is therefore warranted, in particular the role of intrinsic self-inhibition in networks underlying EEG activity associated with alternative paradigms (e.g. event-related potentials), and in individuals with DS with cognitive decline or dementia. Further development of the DCM model detailed here may assist with drug discovery. General ethical considerations relating to cognitive enhancement in DS are also outlined.

Declaration	2
Abstract	3
Thesis overview	4
List of tables.....	8
List of figures	9
Declaration of contributions	10
Acknowledgements	11
Chapter 1 Down syndrome introduction.....	12
1.1 Down syndrome	12
1.1.1 Etymology	12
1.1.2 Epidemiology	12
1.1.3 Phenotypic features	13
1.2 Neurobiological features of Down syndrome	14
1.2.1 Neuroanatomical, cellular and neuropathological features	14
1.2.2 Excitation/inhibition balance	15
1.2.3 Connectivity	16
1.3 Cognitive profile in Down syndrome	16
1.3.1 General cognitive profile.....	16
1.3.2 Age-related changes in cognition	20
1.3.3 Cognitive testing in DS	22
Chapter 2 Electroencephalography (EEG) introduction.....	28
2.1 EEG background information	28
2.2 Resting-state EEG.....	30
2.3 Resting-state EEG and cognition in the TD population.....	33
2.3.1 Delta and theta activity	33
2.3.3 Alpha activity	34
2.3.4 Beta and gamma activity	35
2.4 Literature review: Resting-state EEG in individuals with DS.....	36
2.4.1 Background information and systematic literature review	36
2.4.2 Resting-state EEG characteristics associated with DS	50
2.4.3 Resting-state EEG characteristics associated with cognition in DS	57
2.4.4 Summary and implications	62
2.5 Thesis aims and hypotheses	63
2.5.1 Aims	63
2.5.2 Hypotheses	64
Chapter 3 General Methods	65
3.1 Overall study design.....	65
3.2 Ethical considerations.....	65
3.3 Participant recruitment.....	66
3.3.1 Cognitive assessment	66
3.3.2 EEG assessment	66
3.4 Cognitive assessment	67
3.5 Resting-state EEG paradigms.....	68
3.6 EEG data acquisition	69
3.7 EEG processing	70
3.7.1 Pre-processing	70
3.7.2 EEG measures.....	71
3.8 Data analysis	72
Chapter 4 Analysis of participant sample and paradigm feasibility.....	73
4.1 Introduction.....	73
4.1.2 Aims.....	74
4.2 Methods	75
4.2.1 Participants	75
4.2.2 Cognitive, clinical and demographic variables	76
4.2.3 EEG recording paradigms	76

4.2.4 Statistical analysis.....	77
4.3 Results.....	77
4.3.1 Participant sample.....	77
4.3.2 Dementia prevalence in the EEG sample.....	79
4.3.3 Age and ability in the sample.....	79
4.3.4 Effect of accommodation type in the sample.....	80
4.3.5 Overall paradigm feasibility.....	81
4.3.6 Assessment of EC paradigm feasibility: full block vs. split block.....	83
4.4 Discussion.....	83
4.4.1 Summary of findings.....	84
4.4.2 Research in context, strengths, limitations and future research.....	84
4.4.4 Conclusions.....	86
Chapter 5 Eyes-closed resting-state EEG: comparison between adults with Down syndrome and typically-developing controls.....	88
5.1 Introduction.....	88
5.1.2 Aims and hypotheses.....	90
5.2 Methods.....	90
5.2.1 Participants.....	91
5.2.2 EEG acquisition.....	91
5.2.3 EEG processing and analysis.....	92
5.2.4 Statistics and visualisation.....	93
5.3 Results.....	94
5.3.1 Preliminary analysis.....	94
5.3.2 EEG variables within DS and control groups.....	94
5.3.3 Statistical comparison of EEG variables between DS and control groups...	97
5.4 Discussion.....	101
5.4.1 Summary of findings.....	101
5.4.2 Research in context.....	103
5.4.3 Limitations, strengths and future research.....	105
5.4.4 Conclusions.....	107
Chapter 6 Within Down syndrome EEG correlates of general cognitive ability.....	108
6.1 Introduction.....	108
6.1.1 Frequency.....	108
6.1.2 Power.....	108
6.1.3 Reactivity.....	109
6.1.4 Age-related change.....	110
6.1.5 Aims and hypotheses.....	110
6.2 Methods.....	112
6.2.1 Participants.....	112
6.2.2 EEG analysis.....	112
6.2.3 Statistics and visualisation.....	113
6.3 Results.....	113
6.3.1 Participants.....	114
6.3.2 Eyes-open paradigm.....	114
6.3.3 Eyes-closed paradigm.....	122
6.3.4 Overall results summary.....	129
6.4 Discussion.....	129
6.4.1 Summary of findings.....	129
6.4.2 General cognitive ability.....	131
6.4.3 Predictors of EEG activity.....	134
6.4.4 Regional differences.....	137
6.4.6 Strengths, limitations and future research.....	138
6.4.7 Conclusions.....	141
Chapter 7 Dynamic causal modelling of EEG activity.....	142

7.1 Introduction	142
7.1.1 Dynamic Causal Modelling	142
7.1.2 Excitation/Inhibition balance in DS	143
7.1.3 Aim and hypotheses.....	144
7.2 Methods	145
7.2.1 Participants	145
7.2.2 EEG procedures.....	145
7.2.3 DCM procedures	146
7.3 Results	151
7.4 Discussion	154
7.4.1 Summary of findings.....	154
7.4.2 Research in context.....	154
7.4.3 Strengths, limitations and future work.....	156
7.4.4 Conclusions	159
Chapter 8 Overall discussion	161
8.1 Overall summary of key findings	161
8.1.1 Aim 1: Feasibility and generalisability of resting-state EEG recordings.....	161
8.1.2 Aim 2: differences in EEG activity between adults with DS and matched TD controls	162
8.1.3 Aim 3: EEG measures related to age and general cognitive ability	163
8.1.4 Aim 4: Potential cortical circuitry underlying 4-13 Hz activity associated with general cognitive ability and age	163
8.2 Overall interpretation of findings	164
8.3 Overall research in context	165
8.4 Remaining questions and future directions	167
8.4.1 Concept of general cognitive ability	167
8.4.2 Influence of other variables	168
8.4.3 Exploration of delta activity	168
8.4.4 Lifespan analysis.....	168
8.4.5 Cognitive impairment in the TD population	169
8.4.6 Drug exploration.....	170
8.4.7 Ethical implications.....	170
8.5 Conclusions	171
Bibliography	172

List of tables

Table 1.1 Reported prevalence rates of dementia in individuals with DS	21
Table 1.2 Tests of general cognitive ability utilised by studies within the DS population.	23
Table 2.1 Summary of studies in literature review	49
Table 4.1 Participant demographic information.....	78
Table 4.2 Age and KBIT-2 score group comparison	80
Table 4.3 Demographic information relating to obtained data.....	81
Table 4.4 Segments obtained	82
Table 4.5 Demographic information for each EC paradigm	83
Table 5.1 Participant demographics for each group.....	94
Table 5.2 EEG values for each group	95
Table 5.3 Occipital region group comparison.....	99
Table 5.4 Frontal region group comparison	101
Table 6.1 Participant demographics.....	114

Table 6.2 EO occipital multiple regression power and alpha peak results	117
Table 6.3 EO Frontal multiple regression power and alpha peak results	119
Table 6.4 EC occipital multiple regression power, alpha peak and alpha reactivity (4-13 Hz) results	125
Table 6.5 EC frontal multiple regression power and alpha peak results	128
Table 6.6 Summary of results	129

List of figures

Figure 1.1 Percentage of participants at floor for KBIT-2 subscales	24
Figure 1.2 Previous reports of KBIT-2 raw score in individuals with DS	25
Figure 2.1 Diagram of current dipoles in the cortex	29
Figure 2.2 EEG resting-state publications over time	30
Figure 2.3 Diagram of EEG frequency bands	31
Figure 3.1 EEG electrode map.....	70
Figure 4.1 EEG participant flow diagram	74
Figure 4.2 Number of participants at each pathway stage	78
Figure 5.1 Electrode map illustrating occipital and frontal montages	93
Figure 5.2 DS power-frequency spectra	96
Figure 5.3 Control power-frequency spectra.....	97
Figure 5.4 Group comparison of power-frequency spectra	98
Figure 6.1 EO power-frequency spectra	115
Figure 6.2 Panel of graphs showing significant relationships found for EO Occipital EEG data.....	118
Figure 6.3 Panel of graphs showing significant relationships found for EO Frontal EEG data.	120
Figure 6.4 EO power-frequency spectrum for median split KBIT-2.....	120
Figure 6.5 EC power-frequency spectra	122
Figure 6.6 Comparison between EO and EC power-frequency spectra.....	123
Figure 6.7 Panel of graphs showing significant relationships found for EC Occipital EEG data.....	125
Figure 6.8 EC power-frequency spectrum for median split KBIT-2	126
Figure 7.1 Network nodes.....	147
Figure 7.2 Microcircuit model within each node	148
Figure 7.3 Candidate models.....	150
Figure 7.4 Individual subject model fits	151
Figure 7.5 Selected model	152
Figure 7.6 Intrinsic self-inhibition.....	153

Declaration of contributions

Throughout this work I have received supervision and advice from my PhD supervisors Andre Strydom and Carla Startin. Ethical approval of the study was obtained by Carla Startin, Andre Strydom and Tarama Al-Janabi. Recruitment for the cognitive assessment sessions was performed by myself, Carla Startin and Ros Hithersay, with additional assistance provided by Lucy Fodor-Wynne. Recruitment for the EEG assessment sessions was performed by myself.

The larger LonDownS study in which this project is nested in, and through which cognitive data was obtained for the purpose of this study, was designed by Andre Strydom. The EEG study was designed by Carla Startin and myself, with input from Andre Strydom and Michelle de Haan. The specific EEG paradigms used in this study were designed and programmed by myself, with advice and assistance from Carla Startin and Michelle de Haan.

Two researchers were required to carry out each cognitive assessment and each EEG assessment with every participant. I undertook approximately half of all cognitive testing sessions, with the help of either Carla Startin, Ros Hithersay, or an assisting student (Erin Rodger, Amy Davies, Bryony Lowe or Nidhi Aggarwal). I undertook all EEG sessions, with assistance from Carla Startin.

I obtained approximately half of the genetic samples used in this study from participants (blood or saliva sample). Genotype processing was performed by John Hardy's laboratory and trisomy status was determined by Kin Mok.

For chapters 5 and 6, I collaborated with Dan Bush to create a customised MATLAB script to extract alpha peak and band power measures from each participant, and to plot power-frequency spectra. I further edited this script to enable it to extract all EEG measures and plot all power-frequency spectra I required for these two chapters.

For chapter 7, I collaborated with Richard Rosch to perform DCM analysis. Results were interpreted by myself with input from Richard Rosch and Karl Friston, in addition to members of Karl Friston's research group on the two occasions I presented at their lab meeting.

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Chapter 1 Down syndrome introduction

1.1 Down syndrome

1.1.1 Etymology

Down syndrome (DS) was first described in 1862 by the English physician John Langdon Down. He used the term “Mongolian idiocy” to describe a subset of his patients at the Royal Earlswood Asylum for Idiots. DS was known by this name, with individuals referred to as “Mongoloids”, until 1961 when the Lancet ran a letter to the Editor from 19 noted geneticists calling for the condition to be renamed due to racial connotations (Allen et al., 1961). A number of names were suggested (including trisomy 21 as a consequence of the 1959 discovery that DS was caused by the presence of an extra copy of chromosome 21). From the options presented the Editors selected “Down’s syndrome” and in 1965 the World Health Organisation adopted this renaming. More recently the preferred term has become “Down syndrome”. The condition may also be referred to as “trisomy 21”. Clinically and in general language the term “Down syndrome” is used more often, whereas “trisomy 21” is more commonly utilised when discussing underlying biological mechanisms.

1.1.2 Epidemiology

In countries where elective terminations are permitted, a large proportion of pregnancies with a diagnosis of DS end in termination. Results from a systematic review report this is as high as 92-100% in the UK, and between 87-98% in the US (Mansfield et al., 1999). However, a more recent population modelling study in the US has estimated elective termination rates to be 30% (de Graaf et al., 2015). Similar population modelling estimates have not been carried out in the UK.

Despite high elective termination figures, DS is the leading genetic cause of intellectual disability (ID) worldwide, estimated to affect 1 in every 800 births (de Graaf et al., 2015). At present this number is increasing due to a rise in maternal and paternal age at conception, which are both important risk factors for DS (Coppedè, 2016). In addition to this, people with DS are living longer due to advances in medical treatment and care; the average life expectancy in the developed world for an individual born with DS has increased from below age 10 in the 1970s to age 50 in 2010, with around 1 in 10 individuals now reaching age 70 (Presson et al., 2013).

According to a meta-analysis by Wu & Morris (2013), in 2011 in England and Wales the population prevalence of DS was estimated at 0.66 per 1000 people (in total an estimated 37,090 were living with DS). The average life expectancy of babies born with DS in 2011 was estimated to be 51 years. It was reported by the authors that there is a particularly large proportion of individuals with DS in their 40s, owing to sudden increases in the survival of babies with DS in England and Wales in the 1950s.

There are a number of different genetic causes of DS. The above values refer to all forms of DS; population prevalence figures are not available for individual forms. It is, however, estimated that of all individuals with DS, 95% of individuals have full trisomy 21 (a complete extra copy of chromosome 21). The remaining 5% includes individuals with a translocation (where part of chromosome 21 is attached to another chromosome), partial trisomy 21 (only a portion of chromosome 21 is duplicated), or mosaicism (only some cells have an extra copy of chromosome 21) (Hernandez & Fisher, 1996).

1.1.3 Phenotypic features

The presence of an extra copy of chromosome 21 in individuals with DS leads to an “extra dose” of the genes located on this chromosome. It is this extra dose that is believed to cause the phenotypic features of DS. These features include physical characteristics and increased incidence of specific clinical conditions, in addition to physical and intellectual disabilities. The expression of DS phenotypic traits is highly variable, particularly in rarer forms of DS. For example some individuals with mosaic DS may have a near-typical phenotype depending on percentage of cells and tissue type affected (Papavassil et al., 2014).

The most common phenotypic traits in DS are classic facial appearance (i.e. small nose, flat nasal bridge, eyes that slant upwards and outward), hypotonia and ID (IQ < 70). The cognitive phenotype of DS is discussed in detail below (section 1.3). It is typified by ID (mean IQ approximately 50), delays in reaching developmental milestones, and specific deficits in language and memory domains. There is a great degree of variability, however, between individuals with DS in terms of cognitive profile. Additionally, variability in IQ exists within individuals across the lifespan (generally appearing to decline across adulthood).

Other phenotypic traits include congenital heart defects (present in around 60% of individuals with DS) and a 10-30-fold increased risk of leukemia (Hernandez & Fisher, 1996). Individuals with DS are also at an ultra-high risk of developing Alzheimer's disease (AD), with lifetime prevalence estimated to be as high as 90% (McCarron et al., 2014). This is thought to be due to the over-expression of the amyloid precursor gene (APP) on chromosome 21. Consistent with this, amyloid deposits are present in the brains of almost all adults with DS over the age of 35 (Mann, 1988; Wisniewski et al., 1985).

Individuals with DS are also at increased risk of developing autoimmune conditions, including hypothyroidism, alopecia, celiac disease and type 1 diabetes (Whooten et al., 2018). Due to increased incidence of autoimmune conditions, in addition to reports of poor immune function, intrinsic alteration of the immune system in individuals with DS has been proposed (Guaraldi et al., 2017).

Sensory impairments are common in individuals with DS. It is estimated that 80% of children with DS show problems with vision, including refractive errors, nystagmus and/or strabismus (Roizen & Patterson, 2003). Cataracts are also common (72% of adults; Fong et al., 2013). Additionally, an estimated 40-80% of individuals with DS experience hearing loss (Roizen and Patterson, 2003).

1.2 Neurobiological features of Down syndrome

1.2.1 Neuroanatomical, cellular and neuropathological features

Neurodevelopment in DS is relatively typical up to the first few months of life but then slows (Wisniewski & Schmidt-Sidor, 1989), leading to reduced white and grey matter volume within various regions of the adult brain. DS is characterised by a marked reduction in brain size compared to individuals from the typically-developing (TD) population. In particular the volume of the cerebellum, prefrontal cortex, and hippocampal regions are particularly reduced (Baxter et al., 2000; Pinter et al., 2001; Teipel et al., 2003; Guidi et al., 2011; Carducci et al., 2013).

At a cellular level, reduced cerebellar volume is thought to be due to reduced granule and purkinje cell numbers. In the cerebral cortex, reduced cell numbers (particularly granule cells) in cortical layers 2 and 4 are commonly reported, in addition to malformed and atrophic dendritic trees (Wisniewski et al., 1990; Becker et al., 1993).

Cellular atypicalities that are likely to reduce neuronal transmission have also been described in DS, including fewer synapses, delayed myelination, and altered electrophysiological properties of neuronal cell membranes (Wisniewski et al., 1990; Becker et al., 1993).

The reduced number of neurons in DS has been linked to abnormalities in neuronal differentiation – DS neural progenitor cells show reduced acquisition of a neuronal phenotype. Instead, acquisition of an astrocytic phenotype is increased (Stagni et al., 2018). For this reason individuals with DS have greater cortical astrocyte density compared to individuals from the TD population. Additionally, abnormalities in DS astrocyte function have been reported, including higher levels of reactive oxygen species and lower levels of synaptogenic molecules (Chen et al., 2014).

As previously mentioned, AD-related neuropathology in the form of amyloid deposits are almost ubiquitous in adults with DS over the age of 35 (linked to over-expression of the APP gene on chromosome 21). Neurofibrillary tangles composed of phosphorylated tau are also found in adults with DS (linked to an over-expression of Dyrk1A and RCAN1 genes, also found on chromosome 21) (Kasai et al., 2017). Accordingly, age-related changes that take place in DS across adulthood are almost identical to AD-related neuropathological changes within the TD population (Kasai et al., 2017).

1.2.2 Excitation/inhibition balance

At present there is a strong focus within mouse model studies of DS on imbalance of excitatory/inhibitory (E/I) processes, and GABAergic over-inhibition has recently been proposed as a hypothesis for cognitive deficit in DS (Zorrilla de San Martin et al., 2018). The importance of E/I imbalance has also recently been highlighted in regard to other neurodevelopmental disorders, including autism and schizophrenia (Foss-Feig et al., 2017; Dickinson et al., 2016). Evidence for E/I imbalance in DS comes from mouse model studies (Ts65Dn mice) which have reported increased numbers of GABAergic interneurons and enhanced interneuron excitability, enhanced GABAergic differentiation of neuronal progenitor cells, and alterations in cortical glutamatergic transmission (Chakrabarti et al., 2007; Chakrabarti et al., 2010; Pérez-Cremades et al., 2010; Hernández et al., 2012; Mazur-Kolecka et al., 2012; Tyler & Haydar, 2013; Guidi et al., 2014; Hernández-González et al., 2015; Contestabile et al., 2017).

Overall results are suggestive of a shift in the balance of E/I within Ts65Dn mice to a state of over-inhibition. However, studies involving humans and human tissue from individuals with DS contradict these findings and instead are suggestive of reduced inhibition in DS (e.g. Bhattacharyya et al., 2009; Smigielska-Kuzia et al., 2010). The hypothesis of E/I imbalance in DS will be discussed further in Chapter 7.

1.2.3 Connectivity

At present published research into brain connectivity in DS is limited, however atypicalities in structural connectivity, functional connectivity and network organisation have been demonstrated in individuals with DS (pre-dementia) compared to age-matched TD control subjects. In particular it has been reported that individuals with DS exhibit reduced white matter connectivity in all major white matter pathways, with the strongest differences found in frontal-subcortical circuits (as measured by diffusion tensor imaging (DTI); Fenoll et al., 2017). Studies of functional connectivity using fMRI have demonstrated higher connectivity within the ventral network and lower connectivity in the dorsal network in individuals with DS (Pujol et al., 2015). fMRI studies have also indicated individuals with DS show widespread increased synchrony between brain regions, with a small subset of distant connections exhibiting under-connectivity (Anderson et al., 2013). EEG has also been used in one study to examine functional connectivity in children with DS, with disruptions of functional connectivity within alpha and theta bands reported (Ahmadlou et al., 2013). Additionally, Anderson et al. (2013) and Ahmadlou et al. (2013) examined network organisation using fMRI and EEG respectively. Together these studies reported that individuals with DS exhibit simplified and random network structures, that deviate from an optimal “small-world” network structure found in the TD population.

1.3 Cognitive profile in Down syndrome

1.3.1 General cognitive profile

1.3.1.1 *Global intelligence*

Intelligence quotient (IQ) refers to the total score derived from standardised tests of intelligence. There are many such tests available; some of which combine verbal and

non-verbal abilities to form a composite IQ score, whereas other focus on either verbal or non-verbal IQ subscales. Measurement of IQ in DS is discussed in detail under “1.3.3 Cognitive testing in DS” below.

In general, standard IQ tests are scaled so the mean value is 100; one standard deviation is 15 points and two standard deviations are 30 points. An IQ of 70 (two standard deviations from the mean) is typically used to define a global deficit in intellectual functioning for the purpose of ID diagnosis. As previously mentioned, DS is the most common genetic cause of ID. According to the most recent Diagnostic and Statistical Manual of Mental Disorders (DSM-V; 2013), in order for an individual to meet the criteria for ID they must exhibit deficits in both intellectual functioning (IQ < 70) and adaptive functioning (such as personal independence or communication skills), evident during childhood or adolescence.

Global intellectual impairment is considered a characteristic feature of DS and almost all individuals have an ID (Vicari et al., 2005; Constestabile et al., 2010). Mean IQ reported in studies utilising full-scale standardised IQ scores varies within the literature from 39 (Leiter-R scale; d’Ardhuy et al., 2015) to 60 (Stanford-Binet scale; Carmeli et al., 2002). Studies using the Wechsler Adult Intelligence Scale (WAIS) have reported a mean IQ score of 45 (Edgin et al., 2010) and 50 (Breia et al., 2014). Despite this a small number of individuals with DS have an IQ that is beyond 70 (e.g. Edgin et al., 2010). Additionally individuals with rarer forms of DS, such as mosaicism, may not exhibit significant intellectual impairment (e.g. Fishler & Koch R, 1991).

1.3.1.2 Specific domains

In addition to such global impairments, deficits in specific domains contribute to the general cognitive profile of DS at the group-level. These include deficits in memory, language and executive functions. Importantly, deficits in each of these domains can in turn adversely impact other aspects of cognition. For example, it is hypothesised that deficits in verbal processing in DS are a result of phonological loop deficits – an aspect of working memory (Grieco et al., 2015).

Memory impairments in DS include both short-term and working memory deficits, in addition to long-term memory difficulties (Vicari et al., 2000; Nadel, 2003; Kogan et al., 2009). One particular aspect of the cognitive profile in DS is that non-verbal abilities are generally relatively stronger than verbal abilities. Consistent with this, visual learning

and memory has been demonstrated as stronger than verbal learning and memory at a group level (Grieco et al., 2015).

Both language comprehension and speech production are impaired in individuals with DS. Specific language impairments include deficits in articulation, phonological processing and morphosyntax (Grieco et al., 2015). Although deficits in semantic, pragmatic, and communicative intent are said to be relatively preserved in adults with DS, impairments are still present in these abilities compared to TD individuals (Bello et al., 2014).

Numerous aspects of executive functioning (EF) are impaired in individuals with DS relative to age-matched TD individuals, including attention, inhibition, speed of processing, working memory, planning, set-shifting and self-monitoring. This is consistent with a pattern of global executive dysfunction (Grieco et al., 2015).

Specifically, deficits have been demonstrated in response inhibition (Edgin et al., 2010; Lanfranchi et al., 2010); in particular with verbal relative to visual tasks (Borella et al., 2013; Costanzo et al., 2013). Deficits have also been demonstrated in inhibition of irrelevant information (Cornish et al., 2007; Borella et al., 2013). Both auditory and visuospatial working memory is impaired in DS; although impairments in auditory working memory are more severe (Frenkel & Bourdin, 2009; Lott & Dierssen, 2010; Levy & Eilam, 2013). It is said that visuospatial working memory is relatively preserved in DS (e.g. Grieco et al., 2015). Interesting, although individuals with DS generally take longer to execute actions in planning tasks, accuracy of performance on planning tasks has been demonstrated as similar to mentally-age matched control subjects (Vicari et al., 2000; Pennington et al., 2003; Rowe et al., 2006). Finally set-shifting – especially on verbal tasks – is particularly challenging for individuals with DS (Rowe et al., 2006; Costanzo et al., 2013).

This specific pattern of cognitive impairment in DS is not only demonstrated in respect to TD control subjects but also relative to individuals with other forms of ID, even when matched for level of cognitive functioning (e.g. fragile X; Grieco et al., 2015). This suggests the DS cognitive phenotype is distinct. Despite the fairly well characterised cognitive profile in DS described here, a large degree of variability exists between individuals, with relative strengths and weaknesses occurring within this profile on an individual basis (Grieco et al., 2015).

1.3.1.3 Mechanisms

Specific neurobiological mechanisms underlying the general cognitive profile in DS are unclear, however a number of potential contributing factors have been proposed. At the neuroanatomical level, memory and EF impairments have been associated with reduced volume of the hippocampus and prefrontal cortex respectively (Carducci et al., 2013; Pinter et al., 2001; Teipel et al., 2003). Recently proposed neurobiological mechanisms underlying cognitive impairment in DS include the influence of specific single gene candidates, in addition to global E/I imbalances.

Evidence for neurobiological mechanisms is provided by mouse model studies. For example, several mouse models of DS exhibit hippocampal long-term potentiation (LTP) deficits and enhanced long-term depression (LTD) relative to control mice (Zorrilla de San Martin et al., 2018). Further investigation has shown these features may be a downstream consequence of excessive GABAergic activity (Kleschevnikov et al., 2004). As the integration of synaptic inputs and changes in synaptic strength – mediated by LTP/LTD processes – are proposed as the cellular basis of learning and memory (Pastalkova et al., 2006), impairments in these processes are likely to substantially impact on cognition. Additionally, this fits with the hypothesis that long-term memory impairments in DS may occur at the level of encoding (Carlesimo et al., 1997). E/I imbalance may therefore be an important mechanism underlying cognitive deficit in DS.

Single gene candidates have also been the focus of recent research. For example, the gene DYRK1A (dual-specificity tyrosine phosphorylation-regulated kinase 1A) is involved in neurobiological processes that are altered in DS (e.g. neurogenesis and neuronal differentiation; Hämmerle et al., 2003), and in the early onset of AD (Wegiel et al., 2011). DYRK1A is overexpressed in individuals with DS and in mouse models of DS (Guimera et al., 1999; Dowjat et al., 2007). Recent studies normalising the number of copies of this gene in mouse models of DS have demonstrated improvements in hippocampal-dependent learning (Garcia-Cerro et al., 2017; Jiang et al., 2015). Authors have proposed the recovery of synaptic plasticity as one potential mechanism mediating this cognitive improvement. Initially this gene was selected based on the investigation of candidate genes from individuals with a rare form of DS (partial duplication of chromosome 21). Investigation of such individuals has led to the identification of a small region on chromosome 21 (containing only 33 genes) that is thought to play a major role in the DS phenotype (Duchon & Herault, 2016). It seems

likely that the investigation of individuals with such rare forms of DS will further enhance our understanding of the impact of individual genes on cognition in DS.

1.3.2 Age-related changes in cognition

In addition to variability in cognitive profile between individuals with DS, variability may also occur across the lifespan on an individual basis. In general, cognitive growth occurs in individuals with DS throughout childhood, adolescence and early adulthood, and is then followed by decline in standardised test scores and a gradual loss of abilities (e.g. Hauser-Cram et al., 1999; Couzens et al., 2011).

Decline in older adults with DS is typically associated with AD-neuropathology. However, decline may also occur due to mental health factors such as depression, or physical health conditions such as hypothyroidism or problems with hearing and vision. Although rare, young adults with DS may experience a sudden episode of decline known as “regression”. This was recently characterised by Worley et al. (2015) and termed Down Syndrome Disintegrative Disorder.

Older adults with DS are at an ultra-high risk of developing AD-like dementia. Early neuropathological studies tended to suggest that all individuals with DS develop AD (e.g. Mann 1988; Dalton & Wisniewski 1990), however population prevalence studies argue against this (see Table 1). Recent lifetime estimates are as high as 90% (McCarron et al., 2014).

The average age of dementia diagnosis in individuals with DS is around 55 years (McCarron et al., 2014), however great variation exists in age of onset. For example, some individuals receive a diagnosis in their 30s whereas others may not develop dementia until their 60s, and some individuals may still not have developed dementia in their 70s (see Table 1.1).

Study	Location	Assessment method	Prevalence by group
Visser et al., 1997	Netherlands	Early Signs of Dementia Checklist and the Social Skills Inventory for the Mentally Retarded	11% age 40-49 (n=10); 80% age 50-69 (n=33); 91% age 60-69 (n=20); 100% age 70+ (n=2)
Holland et al., 1998	Cambridge, UK	Clinical criteria (DSM-IV and ICD-10) and modified version of Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)	3.4% age 30-39 (n=29); 10.3% age 40-49 (n=29); 40.0% age 50-59 (n=15)

Sekijima et al. (1998)	Nagano Prefecture, Japan	Observations in daily activities for at least 1 year	0.0% age 30-39 (n=39); 16.3% age 40-49 (n=43); 40.9% age 50-59 (n=22) 0.0% age 60+ (n=2)
Van Buggenhout et al. (1999)	Netherlands	Dementia Questionnaire for Mentally Retarded Persons, Observation List for Aging Residents, Sociale Redzaamheidsschaal (Daily Living Skills)	0.0% age 30-39 (n=16); 11.1% age 40-49 (n=35); 42.2% age 50-59 (n=29) 0.0% age 60+ (n=1)
Tyrrell et al., 2001	Ireland	Modified DSM-IV criteria; Daily Living Skills Questionnaire (DLSQ); Test for severe impairment (TSI); Down syndrome Mental Status Examination (DSMSE)	1.4% age 35-39 (n=70); 5.7% age 40-49 (n=122); 30.4% age 50-59 (n=79); 41.7% age 60-69 (n=12); 50.0% age 70+ (n=2)
Coppus et al., 2006	Netherlands	ICD-10 criteria and Ageing Special Interest Group of the International Association for the Scientific Study of Intellectual Disabilities (IASSID) guidelines	8.9% age 45-49 (n=9); 17.7% age 50-54 (n=17); 32.1% age 55-59 (n=33); 25.6% age 60+ (n=29)

Table 1.1 Reported prevalence rates of dementia in individuals with DS

Percentage of individuals with a diagnosis of dementia is shown for each age group reported, out of the total number of individuals per group (n). Assessment method refers to primary method of dementia diagnosis used by each study.

Variation in reported age of onset may be in part due to differences in assessment method and difficulties identifying cognitive decline in individuals with DS (discussed in more detail below). Evidence also suggests initial signs of decline in some individuals with DS may be atypical. For example, impairments in EF may be the first observable sign of dementia in many individuals with DS (e.g. apathy, impaired planning or problems with attention; Rowe et al., 2006; Ball et al., 2008). It has been proposed that attentional impairments in individuals with DS may be detected 2 years before dementia diagnosis (Krinsky-McHale et al., 2008).

Prevalence rates may also be influenced by mortality. Dementia is a terminal illness (median survival in DS approximately 7 years after diagnosis; McCarron et al., 2014). The rates reported in Table 1 do not take account of differences in mortality between individuals with and without dementia. Coppus et al. (2006) hypothesised that it was for

this reason that dementia prevalence decreased in their sample after 60 years of age, despite incidence continuing to increase in this age group.

Neuropathologically, post-mortem studies show that all individuals with DS have amyloid plaques and tau tangles that are characteristic of AD by age 35 (Mann, 1988). The predominant hypothesis pertaining to this ultra-high risk of AD is that the amyloid precursor protein (APP) gene, which produces amyloid protein, is found on chromosome 21. Consequently over-expression of this gene (as found in individuals with three copies) leads to amyloid over-production and subsequent deposition (Wiseman et al., 2015). This is similar to studies of early-onset AD in the TD population, where it has been shown that genetic mutations resulting in the over-expression of the APP gene (e.g. APP copy number variations) leads to the formation of amyloid-plaques and subsequent dementia (Goate et al., 1991; Murrell et al., 1991). Factors influencing the variability in time between presence of amyloid pathology in all individuals with DS by age 35, and the later emergence of significant cognitive decline (average age of diagnosis 55), are still unknown.

1.3.3 Cognitive testing in DS

Numerous assessment tools have been employed for measuring cognitive abilities and/or cognitive decline in individuals with DS, with several cognitive test batteries in existence (e.g. Edgin et al. 2010; Startin et al., 2016). The direct assessment of cognition in DS can be problematic, however, due to confounding factors influencing task performance. This includes sensory impairment (e.g. problems with hearing and vision) and difficulties with communication. It is also likely that any task requiring a verbal response (e.g. verbal fluency) may be confounded for individuals with relatively poor verbal abilities. Similarly tasks requiring a motor response may be confounded for individuals with motor impairments. Furthermore, test scores are subject to levels of participant motivation and interest, and therefore do not always reflect true level of ability. It is also important to consider the strong cohort influence within the DS population. Significant changes have taken place in terms of health, education, welfare and support over the past 50 years (including the phasing out of institutions in the UK) and this may influence performance. As such some caution must be taken when using cross-sectional data to compare the performance of younger and older adults with DS.

1.3.3.1 *Measuring general cognitive ability*

A variety of standardised IQ tests have been utilised within the DS population (see Table 1.2). The Kaufman Brief Intelligence Test 2nd edition (KBIT-2; Kaufman & Kaufman, 2004) has been employed by more recent studies (Edgin et al., 2010; de Sola et al., 2015; Sinai et al., 2016; Startin et al., 2016). This is a brief tool providing a measure of both verbal and non-verbal abilities. Raw scores from verbal and non-verbal subscales can be used alone, or in combination to provide a measure of global cognitive ability, or standardised according to chronological age in order to provide a measure of IQ.

Test	Description	Utilised by
Kaufman Brief Intelligence Test 2nd edition (KBIT-2; Kaufman & Kaufman, 2004)	Provides verbal and non-verbal measures of intelligence and overall IQ	de Sola et al., 2015; Edgin et al., 2010; Sinai et al., 2016; Startin et al., 2016
Leiter International Performance Scale-Revised (Leiter-R; Roid & Miller, 1997)	Provides a non-verbal measure of intelligence	d'Ardhuy et al., 2015
Peabody Picture Vocabulary Test (Revised edition or 3 rd edition; PPVT-R or PPVT-III respectively; Dunn & Dunn, 1981; Dunn & Dunn, 1997)	Provides a measure of receptive language ability	Schapiro et al., 1990; Das et al., 1995; Chapman, 2006; Iacono et al., 2010
Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1997)	Provides verbal and non-verbal measures of intelligence and overall IQ	Silverman et al., 2010; Breia et al., 2014
Wechsler Intelligence Scale for Children-Revised (WISC-R; Wechsler, 1974)	Provides verbal and non-verbal measures of intelligence and overall IQ	Devenney et al., 2000; Kittler et al., 2004
Stanford-Binet 3 rd edition (Merrill, 1973)	Provides verbal and non-verbal measures of intelligence and overall IQ	Carmeli et al., 2002; Silverman et al., 2010
Prudhoe Cognitive Function Test (PCFT; Kay et al., 2003)	Developed exclusively for participants with ID to measure cognitive ability	Kay et al., 2003
Woodcock-Johnson Tests of Cognitive Ability-Revised (WJ-R; Woodcock & Johnson, 1989)	A set of tests that provide a measure of cognitive ability and achievement	Patel et al., 2001
Raven's Coloured Progressive Matrices (RCPM; Raven, 2003)	Measures abstract reasoning to provide a measure of non-verbal intelligence	Iacono et al., 2010

Table 1.2 Tests of general cognitive ability utilised by studies within the DS population.

A key issue when obtaining an accurate measure of cognitive ability in individuals with DS is the presence of floor effects (i.e. participants obtaining the lowest score possible

on a test). This is particularly an issue when raw scores are standardised. Floor effects for standardised scores have been reported as high as 61% for the Leiter-R (d’Ardhuy et al., 2015). For the KBIT-2, de Sola et al. (2015) reported a 41.9% floor level for full IQ and Startin et al. (2016) reported floor levels of 66.7% for verbal IQ and 39.4% for non-verbal IQ.

For studies concerned with individual differences in cognitive ability, raw scores may be more useful than standardised scores due to greater range of scores and lower floor effects. Three studies identified reported floor effect levels for raw scores of the KBIT-2 (see Figure 1.1); no floor effects were reported for the verbal subscale (apart from for 5% of individuals with dementia), and moderate floor effects were reported for the non-verbal subscale, which increased substantially in participants with dementia (Edgin et al., 2010; Startin et al., 2016; Sinai et al., 2016).

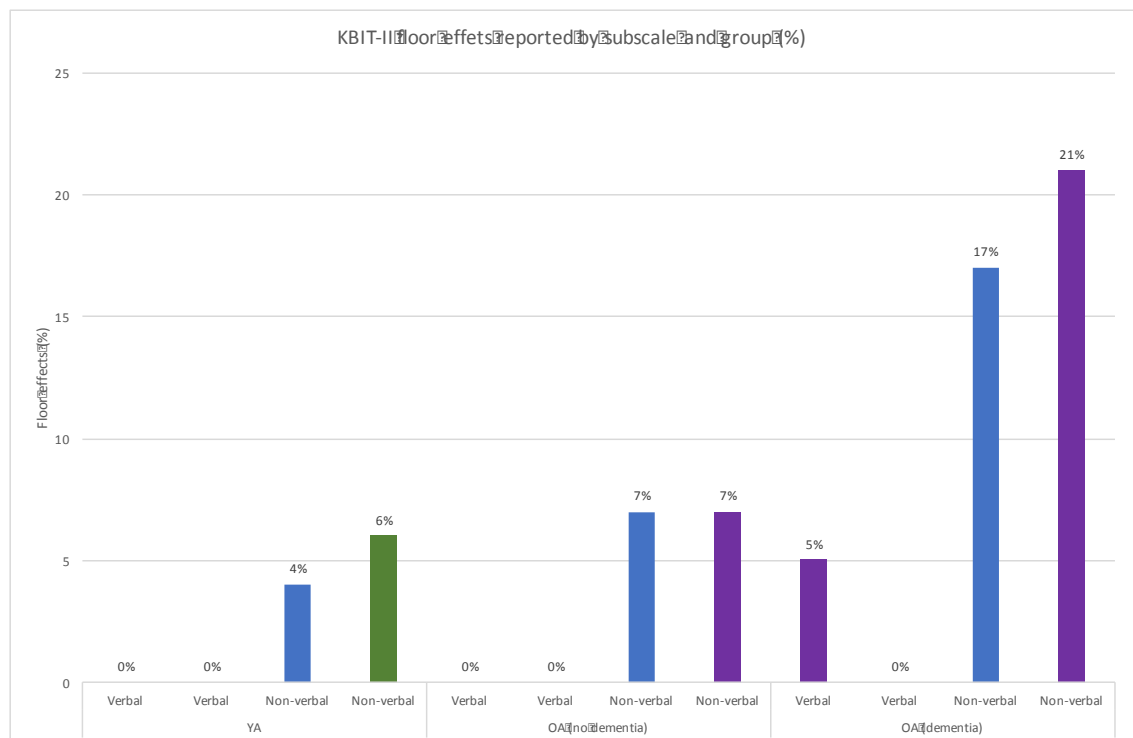


Figure 1.1 Percentage of participants at floor for KBIT-2 subscales

Bar chart showing percentage of participants at floor for KBIT-2 subscales by participant group (younger adults (YA; 16-35 years), older adults (OA without dementia and older adults with dementia; >35 years for Startin et al., 2016; >45 years for Sinai et al., 2016) for individual studies reporting these values (Startin et al., 2016 (blue); Edgin et al., 2010 (green); Sinai et al., 2016 (purple)).

When examining the range of KBIT-2 scores between participant groups using cross-sectional data (see Figure 1.2), verbal and non-verbal subscale means and ranges

reported by Startin et al. (2016) appear relatively stable between younger adults and older adults without dementia, but then decrease in older adults with dementia. Sinai et al. (2016) also reported similar reductions in verbal and non-verbal mean scores and ranges between older adults with dementia compared to older adults without dementia (younger adults were not included in this study). Overall, these studies demonstrate that raw KBIT-2 scores can be obtained from a range of individuals with DS, including many individuals with dementia. It should be noted, however, data displayed in Figure 1.2 is not longitudinal and therefore ability to use this data to draw conclusions about decline in cognitive ability over time is limited.

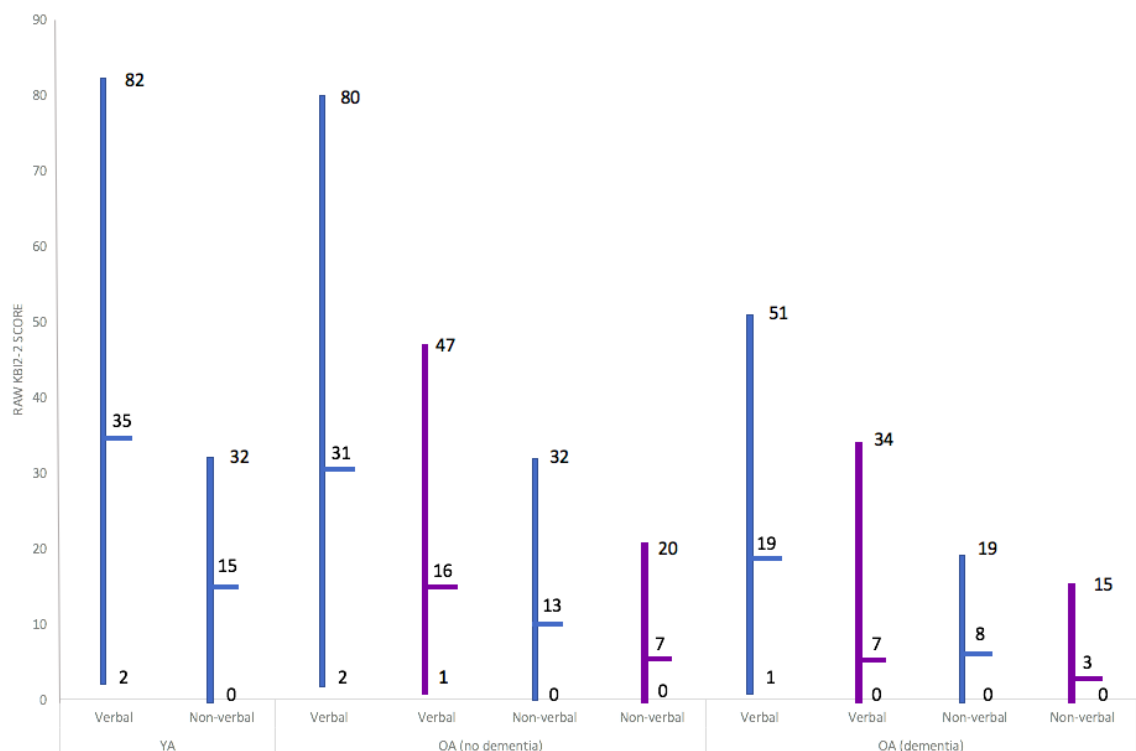


Figure 1.2 Previous reports of KBIT-2 raw score in individuals with DS

Bar chart showing cross-sectional KBIT-2 raw score range and mean by participant group (younger adults, older adults without dementia and older adults with dementia) for individual studies (Startin et al., 2016 (blue); Sinai et al., 2016 (purple)).

1.3.3.2 Measuring cognitive decline

Floor levels are not only an issue when comparing between individuals with DS but also when comparing within individuals over a period of time, for the purpose of assessing cognitive decline. This is because it is not possible to identify decline on a task for which an individual is already at floor. Alternative measures, for example informant questionnaires or measures of adaptive abilities, may be more sensitive to decline in such individuals.

Informant questionnaires are employed within many cognitive test batteries in DS (e.g. Edgin et al., 2010; Sinai et al., 2016; Startin et al., 2016) and are also a key aspect of clinical assessment for the purpose of dementia diagnosis. It is recommended that the assessment of dementia in people with ID should incorporate both direct assessment of the individual and an informant interview (Janicki et al. 1996). In the UK the most commonly used questionnaires in the assessment of cognitive decline in individuals with DS are the Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities (CAMDEX-DS; Ball et al., 2004) and the Dementia Questionnaire for People with Learning Disabilities (DLD; Evenhuis, 1992). The CAMDEX-DS first assesses best level of functioning and then asks about decline in functioning. Later parts of the CAMDEX-DS assess mental and physical health issues. Questions in both tools pertain to similar domains, including memory, orientation, language, everyday skills, mood, behaviour and motivation. The DLD, however, is a screening tool rather than a diagnostic instrument and has poor interrater reliability; only 15% of raters achieved good agreement in a recent study (26 DS individuals; Walker et al., 2014). In contrast, Ball et al. (2004) found good agreement between all raters using the CAMDEX-DS (20 DS individuals; Ball et al., 2004).

Clinical diagnosis of dementia in the TD population requires evidence of a progressive deterioration in memory, in addition to decline in a number of other cognitive domains (e.g. language impairment), and decline in daily living skills (Ball et al., 2004). Full definitions and criteria that are generally accepted are outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association 1994) and the International Classification of Diseases (ICD-10; World Health Organization 1992). Criteria for the diagnosis of dementia in individuals with DS is the same as criteria for the TD population, however decline in functioning must be relative to an individual's baseline level rather than relative to population norms (Ball et al., 2004). This emphasises the importance of baseline and longitudinal assessment in individuals with DS, as a single assessment cannot differentiate between cognitive impairment due to ID or dementia. Also emphasised is the importance of informant interview with individuals who have known the person for a long period of time.

In addition to the above-mentioned issues (the presence of floor effects on formal tests and problems differentiating between impairment due to ID or dementia), difficulties diagnosing dementia in individuals with DS are also encountered due to variability in early symptoms of decline. As mentioned previously, it has been documented that for

some individuals EF impairments may be the first sign of dementia (Rowe et al., 2006; Ball et al., 2008; Krinsky-McHale et al., 2008). This contrasts with the most common early symptoms of dementia in the TD population (impairments in episodic memory and orientation), and upon which DSM-IV and ICD-10 definitions are based. Currently used clinical criteria may therefore not always be the most appropriate method for the identification of dementia in individuals with DS (Ball et al., 2004).

Early diagnosis of dementia in people with DS has important implications for treatment and care. Early diagnosis is also important for clinical trials. Individuals with DS are a particularly important population for clinical trials aimed at preventing dementia due to their ultra-high risk of the disease. Establishing biomarkers for cognitive decline is of substantial value to clinical trials due to the problematic nature of cognitive testing in this population and the possibility that biomarker changes may be observable prior to cognitive changes. It should not be forgotten that biomarkers are also an important tool for clinical trials into treatments aimed at improving cognition in younger adults with DS.

Within the TD population electroencephalography (EEG) features have been linked to cognition (including IQ and memory ability), ageing and dementia (Hughes & Cayaffa, 1977; Coben et al., 1983; Lehtovirta et al., 1996; Klimesch, 1999; Claus et al., 1998; Clark et al., 2004; Moretti et al., 2004). This includes the detection of subtle cognitive changes (discrimination between different types of dementia and conversion from mild cognitive impairment (MCI) to AD; Neto et al., 2015; Poil et al., 2013). It is therefore possible that the EEG signal from individuals with DS may contain features that can be linked to cognitive ability, ageing and cognitive decline in this population. Passive paradigms may prove particularly useful in individuals with DS due to the lack of participant response required, reducing the confounding influences of ID and presence of language and/or motor impairments. This will be considered in more detail in the next section.

Chapter 2 Electroencephalography (EEG) introduction

2.1 EEG background information

The human EEG was first recorded in 1924 by a German psychiatrist named Hans Berger. Berger had worked on the project since the late 1880s, after a near death experience during which he felt that he had communicated with his sister telepathically (Millett, 2001). During his career Berger used EEG to describe different brain rhythms and features of sleep (Berger, 1929). The invention went on to revolutionise the field of clinical neurology. Today EEG has numerous clinical applications, including the diagnosis of seizure and sleep disorders, and monitoring response to anaesthesia (Jameson & Sloan, 2006). It is also an important research tool for studying the brain and cognition.

EEG is a direct measure of ongoing electrical brain activity. The electrical signal recorded at the scalp is thought to mainly reflect the summation of synchronous excitatory and inhibitory postsynaptic potentials of many thousands of cortical neurons (Cohen, 2014). It is estimated that between 10,000 and 50,000 neurons dominate the EEG signal at each electrode (Murakami & Okada 2006; Wang et al. 2005). Superficial pyramidal cells are thought to be the main generators. This is because superficial pyramidal cells are large with an elongated shape, which creates a current dipole between the cell body and dendrites (see Figure 2.1). They are also aligned in parallel to each other. Together these features create an electrical field detectable at the scalp.

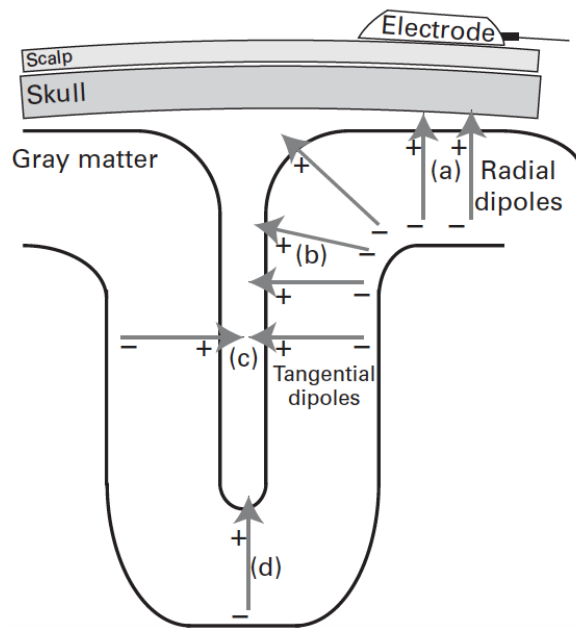


Figure 2.1 Diagram of current dipoles in the cortex

Dipoles are illustrated in different directions with respect to the skull. Radial dipoles (a and d) are the strongest contributors to the detectable signal. Tangential dipoles (c) are likely to cancel each other out, and so are unlikely to be measured. The deeper radial dipole “d” is likely to contribute to the signal, but to a lesser extent than “a” because it is further away from the electrode. Image taken from Cohen, 2014.

A particular strength of EEG is its high temporal resolution. This makes EEG particularly suited to the rapid changes in neural activity that underlie cognitive processes. EEG is also relatively low-cost and has a high degree of tolerability; the latter of which is particularly important in the study of individuals with DS.

EEG has a reputation as a tool with relatively low spatial resolution – electrical activity at each electrode is a summation of not only spatially close sources but many distant sources as well (Makeig et al., 1996). This is because electrical fields in the brain spread and become distorted, particularly through the skull. The ability to determine where in the brain measured signals at the scalp originate is therefore limited. Spatial resolution of scalp EEG is estimated to be 5 – 9 cm (Nunez et al., 1994; Babiloni et al., 2001). With the advent of high-density recording methods and novel analysis methods, however, this problem has been substantially reduced and high-quality source localisation is now deemed possible (e.g. Song et al., 2015).

2.2 Resting-state EEG

The theory that the brain is always active was first proposed by Berger (1929), who reported that electrical oscillations in his subjects did not cease during periods of rest (Gloor, 1969). It was not until this century, however, that the “normal” activity of the brain at rest (that being activity in the absence of any task or controlled stimulation) generated a significant amount of research interest and discussion. It has been reported that before this, “the idea that one would include a resting-state in studies of the human brain was considered unacceptable by cognitive neuroscientists because it completely lacked the features of an adequately designed ‘control state’” (Snyder & Raichle, 2012). The turning point came in 1995, when it was discovered that spontaneous fluctuations in the fMRI signal were not simply noise (e.g. head motion or cardiac pulsations as previously thought), but instead arise from neural activity (Biswal et al., 1995). Following this discovery, baseline levels of activity began to be utilised in studies of evoked cortical responses and also studied in their own right (Cabral et al., 2014). Although resting-state EEG activity had been studied prior to this, this had for the most part been within a clinical context (e.g. the investigation of organic brain disorders). Figure 2.2 illustrates the exponential rise in publications of “resting-state” or “task-free” EEG studies.

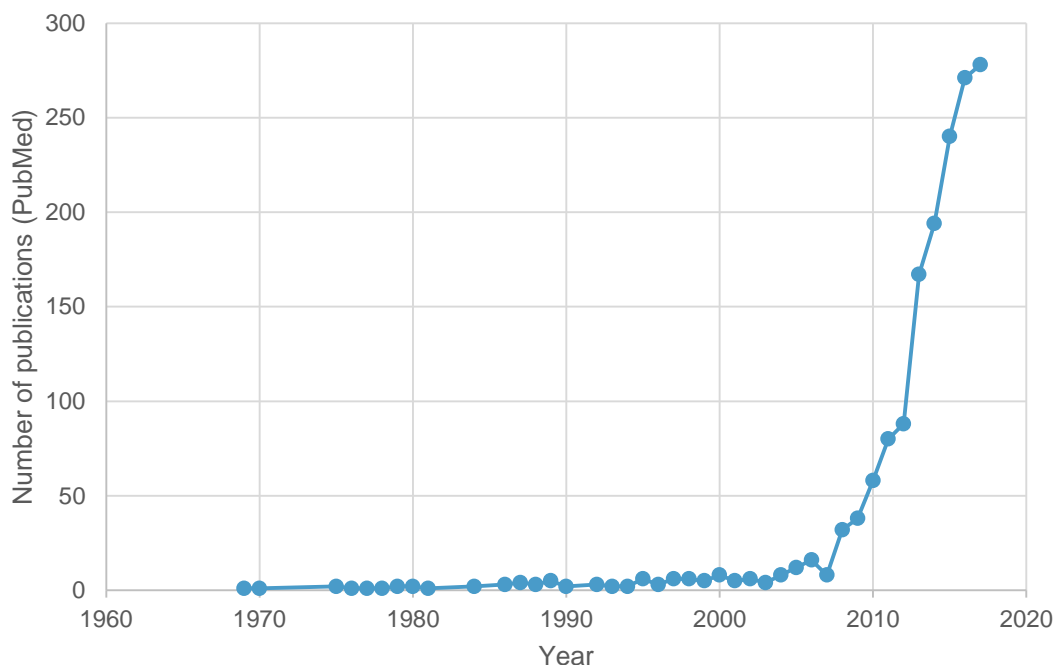


Figure 2.2 EEG resting-state publications over time

Line graph showing number of publications listed on PubMed Central (data downloaded 10/01/18) for each year from 1960 to 2017, using search terms “resting state” or “task free” and “EEG”.

EEG studies examining baseline brain activity employ continuous recording paradigms in either eyes-open (EO) or eyes-closed (EC) conditions. Differences in brain activity occur between EO and EC conditions (particularly around 10Hz; suppression of activity with eye opening), and therefore such experimental differences should be given full consideration during design and interpretation. Resting-state paradigms typically discard temporal information and focus instead on spectral information — that being the frequencies that are present in the signal, in which signals are represented as a linear combination of oscillatory functions (Gross, 2014).

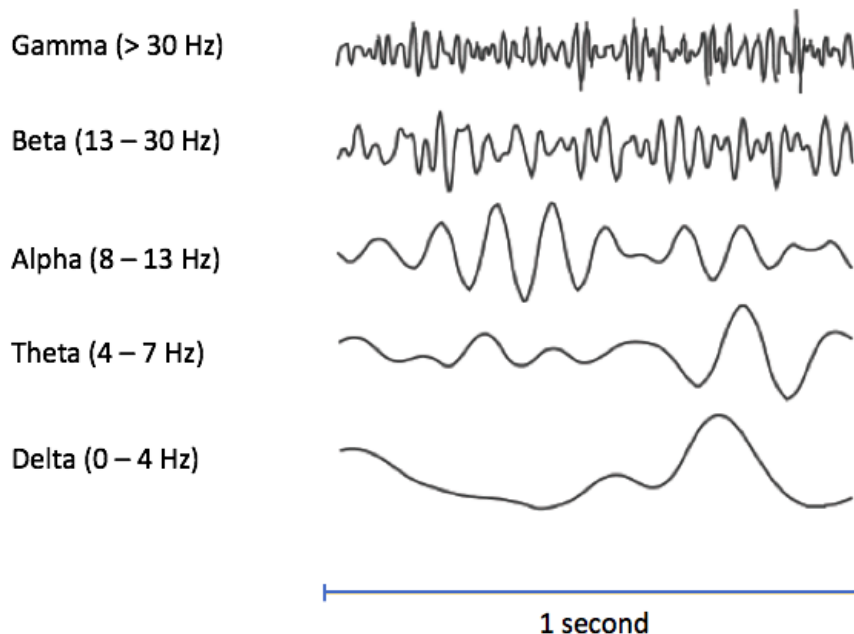


Figure 2.3 Diagram of EEG frequency bands

Diagram illustrating typical EEG activity (over a 1 second period) within each commonly used frequency band: delta (0-4 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (13-30Hz) and gamma (>30Hz) used here.

Existing terms referring to brain rhythms refer to the frequency band the rhythm occupies; typically delta (0-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30Hz) and gamma (>30Hz) (see Figure 2.3). It is of note, however, that brain rhythms do not always operate within such set frequency bands. For instance alpha rhythms are known to operate across a wider frequency range than 8-13 Hz and there is substantial variability between individuals regarding this (Haegens et al., 2014). Some frequency

bands are also commonly subdivided (e.g. upper and lower) to reflect purported differential underlying mechanisms of generation and potential differences between roles in cognition (discussed in more detail under “2.3 Resting-state EEG and cognition in the TD population” below).

Recordings obtained from subjects at rest show activity across the EEG spectrum, amounting to what has been described as “a constellation of brain rhythms” (Buzsaki et al., 2013). It has been proposed that the organisation of these brain rhythms represent the means by which neuronal networks communicate and interact (Buzsaki et al., 2013). For example, the activity of networks of inhibitory interneurons generate rhythmic inhibitory post-synaptic potentials (IPSPs). These rhythmic IPSPs provide windows of alternating reduced and enhanced excitability which offers a temporal framework for the “chunking” of neuronal activity. This “chunking” enables the effective communication of local information to distributed regions. It is posited that these mechanisms enable the brain to integrate a large number of distributed local processes into global states (Buzsaki et al., 2013).

Characterising the constellation of brain rhythms present in an EEG signal is valuable for understanding a wide range of cognitive functions and pathogenic processes. It has been suggested that ‘dysrhythmias’ — reflecting impairments in the temporal organisation of the brain — may underlie many neurological and psychological disorders, including movement disorders, schizophrenia and dementia (e.g. Hutchinson et al., 2004; Spencer et al., 2004; Van Der Stelt et al., 2004; Jeong, 2004). For example in individuals with Schizophrenia, problems in the synchronisation of high-frequency oscillations (as measured by EEG) have been correlated with visual hallucinations and thought disorder (Spencer et al., 2004). EEG rhythms are also known to be differentially affected by a large spectrum of psychotropic drugs (Agid et al., 2007; Alhaj et al., 2011). For example, it has been consistently demonstrated that 5-HT_{1A} receptor agonists (e.g. the commonly used anxiolytic buspirone) produce an increase in theta and decrease in alpha activity (i.e. a negative shift of the EEG spectrum) (Alhaj et al., 2011).

In particular resting-state EEG studies have been important for furthering our understanding of AD (Vecchio et al., 2013); see section “2.3 Resting-state EEG and cognition in the TD population” below. It has been noted that EEG is particularly suited to the study of AD — a cortical dementia — as the cortical field potentials measured by EEG can be directly correlated to pathological changes in the structure and function of cortical layers (Jeong., 2004). In contrast to this, subcortical dementias (such as those

associated with Parkinson's disease and Huntington's disease) exhibit relatively normal EEG patterns (Verma et al., 1987). Accordingly, EEG markers are considered a tool for supporting standard clinical and neurophysiological assessment in AD.

2.3 Resting-state EEG and cognition in the TD population

The relationship between EEG activity and cognition is typically investigated through participants undergoing a battery of cognitive tests separately to an EEG recording, during which event-related and/or resting-state paradigms are employed. Some studies, however, examine task performance during EEG recordings and compare activity between trials (e.g. working memory; Hwang et al., 2005).

2.3.1 Delta and theta activity

Within the TD population few studies have investigated the role of delta activity (typically 0-4 Hz) in cognition. Despite this, delta oscillations measured at the scalp have been implicated in many cognitive processes (Basar et al., 2001; Harmony, 2013). These include attention, motivation, and behavioural inhibition (Knyazev, 2007; Putman, 2011; Harmony, 2013). Delta oscillations are also thought to be involved in the integration of information between distant brain regions, and in the synchronisation of brain activity with autonomic functions (Knyazev et al., 2009; Moran & Hong, 2011).

Research within the TD population suggests that theta activity (typically 4-7 Hz) is associated with memory processes (Osipova et al., 2006; Klimesch, 2012). It has been hypothesised theta oscillations measured at the scalp – in particular over the parietotemporal regions – may indirectly reflect the dynamic interactions that take place between the hippocampal system and cortex (Bastiaansen & Hagoort, 2003).

Multiple studies examining the link between EEG activity and dementia within the TD population report “slowing” of the EEG spectrum – i.e. an increase in slower frequencies (delta, theta) and decrease in faster frequencies (Brenner et al., 1988; Coben et al., 1990; Soininen et al., 1991; Hooijer et al., 1990; Schreier Gasser et al., 1993). It is generally thought that the earliest EEG change observed in AD is an increase in theta activity, whereas delta activity increases occur later (Jeong, 2004).

Mechanistically it has been suggested that cholinergic deficit may be responsible for slowing of the EEG in AD (Jeong, 2004). This is supported by evidence suggesting that

slowing may be induced by anticholinergic drugs (e.g. scopolamine and orphenadrine) and reversed by cholinergic drugs, i.e. acetylcholinesterase inhibitors (e.g. physostigmine, edrophonium chloride and donepezil) (Agnoli et al., 1983; Babiloni et al., 2013).

2.3.3 Alpha activity

Some of the most commonly reported relationships between EEG measures from resting-state data and cognition are those between alpha rhythms (typically 8-13 Hz) and cognitive ability. Alpha rhythms can be found across the scalp of healthy adults but are most visible over the occipital cortex (Niedermeyer, 1997; Hughes & Crunelli, 2005). Alpha was historically thought of as “background” or “idling” activity (an idea first introduced by Adrian & Matthews, 1934), but is now known to underlie and reflect a range of cognitive processes. The main process ascribed to alpha activity is that of an inhibitory attentional filter, with the frequency of oscillations pacing this filter (Klimesch, 2011; Zauner, 2012). It is through this function that alpha is posited to regulate the engagement and disengagement of sensory areas (Haegens et al., 2014).

Alpha activity is sometimes subdivided into two or three frequency bands (i.e. lower-alpha and upper-alpha, or lower (alpha 1), middle (alpha 2), and upper (alpha 3)). Lower alpha (typically below 10 Hz) can be observed in widely distributed networks and is thought to reflect general brain arousal and global attention readiness, whereas upper alpha (typically above 10 Hz) is thought to reflect the oscillations of more selective neural systems and has been associated with memory performance (Steriade & Llinas, 1988; Klass & Brenner, 1995; Klimesch, 1996, 1997, 1998, 1999; Vogt et al., 1998; Rossini et al., 2007). Interestingly differences in the way these sub-bands respond to the neurodegenerative processes of AD and vascular dementia have also been reported (Moretti et al., 2004). In this study individuals with vascular dementia showed reduced alpha 2 power compared to healthy elderly subjects, whereas individuals with AD instead showed reduced alpha 3 power compared to healthy elderly subjects. This indicates the distinction between alpha sub-bands may be relevant clinically.

Studies have reported positive correlations between alpha peak frequency and both IQ (Anokhin & Vogel, 1996) and memory performance (including semantic and verbal) (Klimesch, 1999; Clark et al., 2004). There are sometimes subtle variations in the definition of alpha peak frequency between studies, but typically this term refers to the

frequency associated with the strongest EEG power within the extended alpha range (Klimesch, 1999). It should be noted, however, that although early studies reported a positive correlation between IQ and alpha peak frequency, later studies using larger samples reported no significant relationships (Posthuma et al., 2001). Additionally, some studies have reported negative correlations between IQ and frequency measures (Jaušovec & Jaušovec, 2000).

It is likely significant differences in recording and analysis methods between studies play an important role in inconsistent findings. For example, studies examining more than one region (e.g. Jaušovec & Jaušovec, 2000) may reveal correlations which are not apparent in other (albeit larger) studies that only examine a single region (e.g. Posthuma et al., 2001). Such methodological differences are common among studies investigating EEG characteristics and cognition, making comparison difficult.

Although findings relating to alpha frequency and IQ are inconsistent, a decrease in alpha frequency (alpha slowing) is consistently associated with ageing and also the development of AD (Coben et al., 1983; Lehtovirta et al., 1996). Such slowing has been shown to correlate with AD progression (as measured by mortality) from the earliest stages (Claus et al., 1998).

2.3.4 Beta and gamma activity

Within the TD population few studies have investigated the role of beta activity (typically 13-30 Hz) in cognition. Until recently beta activity was thought to mostly relate to somatosensory and motor functions (Pfurtscheller et al., 1996), however recently it has attracted attention for its potential role in response inhibition (Huster et al., 2013). A decrease in beta activity is also thought to be one of the earliest changes associated with slowing of the EEG spectrum that occurs with AD (Jeong, 2004).

It has been said by Başar et al. (2016) that gamma activity (typically > 30 Hz) does not reflect a specific function of the nervous system but instead is fundamental to all brain functions. Proposed mechanisms through which gamma may be involved in all brain functions include information transmission and the global binding of distributed information (for example, the binding of distributed sensory components into conscious experience) (Buzsaki and Wang, 2012). It is also thought that gamma activity plays important roles in synaptic plasticity (Jensen et al., 2007). In line with the theory that gamma is fundamental to all brain functions, gamma oscillations have been linked to

numerous cognitive processes including perception, attention, working memory, long-term memory, object recognition and emotional paradigms (Jensen et al., 2007; Başar et al., 2016).

2.4 Literature review: Resting-state EEG in individuals with DS

2.4.1 Background information and systematic literature review

2.4.1.1 Resting-state EEG rationale

Understanding the relationship between EEG activity and general cognitive ability in individuals with DS is important for elucidating potential neurophysiological processes underlying cognitive impairment. In turn this may help inform biomarker and drug target search.

Passive paradigms are inherently free from the need to understand and retain instructions relating to response (e.g. to press a button in response to a target). Consequently utilising such tasks reduces the confounding influence of ID level and differences in motor skills on task performance. In addition to resting-state paradigms, a number of passive event-related paradigms (ERP) exist. However, ERP studies are often related to specific cognitive processes. For instance oddball paradigms (where target stimuli are presented amongst more frequent background stimuli and EEG activity associated with each target-type are compared) have been associated with the processes of attention, orientation and memory (Lee et al., 2011). Furthermore these processes are commonly linked to the modality task stimuli are presented within (e.g. visual or auditory). In contrast, resting-state paradigms are considered a more general measure of brain activity, as discussed previously.

Exploring resting-state activity in adults with DS and characterising individual differences in this may also be considered a pre-requisite to fully understanding ERP responses that are potentially downstream of this activity. This is because there is evidence to suggest that resting-state brain activity (particularly alpha activity) may modulate task-based responses (e.g. auditory oddball; Romani et al. 1991; Lee et al., 2011).

2.4.1.2 Historical context

The earliest EEG researchers were interested in the use of EEG to explore electrophysiological characteristics in DS (e.g. Kreezer, 1939; Gunnarson, 1945). Since the end of the Second World War, aside from a small number of studies, very little research was published in this area until the 1990s. It can only be speculated that perhaps the landscape of research into intellectual disability substantially changed after the Nuremberg Code (emphasising individual voluntary consent) was established in 1947. More recently in the UK, the Mental Capacity Act (2005) has supported the inclusion of people with IDs in research by setting a framework for researchers to assess capacity and include those who lack capacity in their research; increasing opportunities for people with DS to be involved in studies. An increase in the number of resting-state EEG studies involving participants with DS is also likely to be influenced by the general increased interest in resting-state EEG outlined in the previous chapter.

2.4.1.3 Identification and screening of studies

Systematic searches of three electronic databases (PubMed, Scopus and Web of Science) were carried out using the following terms: (“Down syndrome”, EEG) or (“Trisomy 21”, EEG). Studies were excluded if all participants were under the age of 16 and were not written in English (translations accepted). Using this criteria a total of 30 studies were identified. Following further inspection, studies were excluded if it was not stated or not clear whether resting-state recordings were obtained under eyes-open or eyes-closed conditions, or if it was not clear which of these conditions results were referring to (n=7; Kreezer, 1939; Gunnarson, 1945; Ellingson & Menolascino, 1967; Uohashi et al., 1970; Ellingson & Lathrop, 1973; Visser et al., 1996; Salem et al., 2015). In the case of the recent study by Salem et al. (2015) the corresponding author was contacted to try obtain this data, however no response was received.

Studies were also excluded if EEG analysis methods were not stated or if methods were restricted to clinical EEG interpretation (e.g. classification of the EEG into normal/abnormal or “conventional impressionistic”) (n=4; Paulson et al., 1969; Ellingson et al., 1973; Crapper et al., 1975; Devinsky et al., 1990). Studies were also excluded when resting-state recordings were obtained during periods of brief awakenings during the investigation of sleep (Clausen et al., 1977). Studies involving both adults and children with DS were excluded where analysis was grouped together, or if it was not clear which age group analyses were referring to (n=3; McAlaster, 1992; Schmid et al., 1992; Johannsen et al., 1996). Two identified studies could not be obtained (Sannita et al., 1993; Kim et al., 2009).

2.4.1.4 Quality and considerations of remaining studies

Following the screening process a total of 13 studies remained (see Table 2.1 for summarised details of participants, methods and results provided by each study). Publication dates ranged from 1970 to 2011. Some of these remaining studies, however, should be reviewed with a level of caution. For instance Ono et al. (1992) excluded 8 participants with DS who had an “undetectable alpha rhythm”. This approach is questionable as overall results from the study (n=36) are not necessarily representative of the wider DS adult population. Furthermore the study by Salamy et al. (1990) is small (n=6) and two studies had eyelids of participants held down during recordings (Babiloni et al., 2009, 2010). The number of participants affected by this is not stated by these studies. Undoubtedly this protocol could cause anxiety and an increased state of vigilance in participants, which have been related to EEG measures (e.g. peak frequency; Jann et al., 2010; Angelakis et al., 2014).

It should be noted that studies by Ono et al. (1992) and Ono (1993) are likely to be the same sample, with the addition of 4 individuals in the second study (n = 36 and 40, respectively). Data collection methods in these papers are identical. The second study, however, incorporates a cognitive test (Activities of Daily Life) and a CT scan (n=21), and standard theta and beta EEG bands are split into upper and lower for the purpose of analysis. Studies by Locatelli et al. (1996) and Medaglini et al. (1997) may also be from the same sample as they are from the same research group, and report identical participant demographics and EEG methodology.

Issues may also arise when comparing findings between the studies identified here. Due to research in this field spanning many decades there is considerable methodological variation between studies. For instance methods of measuring peak frequency differ substantially — early researchers relied on the visual identification of alpha waves from simple montages and calculated frequency by measuring trains of these in length (mm), whereas later studies use a variety of different recording montages, recording sites, frequency measures and frequency bands (e.g. Politoff et al. (1996) measured peak frequency across a 2-20 Hz range). Such differences are a potential source of conflicting results and make comparison problematic.

When reviewing these studies it is also important to consider a number of additional factors. Overall individuals with DS who take part in EEG studies may not be typically

representative of the DS population (e.g. they may be of higher ability and have greater overall health). Research examining the extent that such samples differ is, however, lacking. Additionally, some studies that include older adults with DS do not attempt to control for the possible presence of cognitive decline or dementia (either through clinical criteria or cognitive assessment). Furthermore, in studies that do attempt to control for decline, this in itself may be confounded by level of ID, as discussed previously. Attempting to control for the presence of cognitive decline or dementia is particularly important with studies correlating EEG characteristics with age and/or ability in order to prevent results being confounded by this. Considering younger and older adults separately when investigating the relationship between EEG characteristics and cognitive ability in this population may also help reduce the potentially confounding influence of sub-clinical cognitive decline that may otherwise go undetected.

Title	Authors	Year	Participant description	EEG recording description	EEG analysis description	Additional tests	Summary of reported findings
Neurometric evaluation in down syndrome individuals: possible implications for dual diagnosis	Salamy, Alvarez, Peeke	1990	6 DS subjects (24-78yrs, mean age 42.3yrs)	Eyes-closed, 21 electrode cap, 10/20 system, plus midline and prefrontal (Fpz) leads and electrooculogram leads, 10-15 min recording time (at least 2 mins artifact-free data) acquired and split into 24 to 48 2.5s epochs	Classical frequency bands from both monopolar and bipolar (pairwise central, temporal, parietal-occipital, frontal temporal) recordings were obtained. Absolute power, relative power, symmetry and phase coherence measured. Variables were statistically compared to age appropriate normative values	Further EEG analyses (e.g. multivariate analyses of composite features across frequency bands and electrode locations)	Single exemplary participant had “abundance of theta and delta and marked deficit of alpha and beta” (in terms of absolute and relative power) over much of scalp. This pattern predominated in most of the subjects. NB: Age of exemplary patient unclear.
Age-related changes in occipital alpha rhythm of adults with Down syndrome	Ono, Yoshida, Momotani, Yoshimasu, Higashi	1992	36 DS (aged 15-54, 23 male, mean age 30.7±11.5 yrs), 47 healthy controls (62% male, mean age 30.9±10.8 yrs), 42 non-DS MR (57% male, mean age 30.9±10.8 yrs). 8 additional DS individuals were excluded due to undetectable alpha rhythm	Eyes-closed resting state, 12 channels, 10/20 system	Five artifact-free 5.12 sec duration epochs recorded from left occipital lead (O1-A1) underwent FFT. Calculated peak frequency and relative powers in standard EEG bands (although alpha split into 8-10.5 and 10.5-13 Hz)		Alpha peak frequency was significantly negatively correlated with age in a linear relationship (this was not true of both control groups). There were significant differences Vs controls in alpha frequency for every age group (including age 15-24 yrs). Compared to healthy controls, DS had no diffs in beta, sig decrease in relative power in alpha2 (25-54yrs). OAs (35-54yrs) also had sig increase in theta2 and alpha1. Increases in theta1 were seen in 15-24 and 35-44 age groups. Compared to MR controls

							there were similar alpha1 and alpha2 differences in OA
EEG changes with ageing in adults with Down syndrome	Ono	1993	40 DS (age 15-54, mean 30.3± 11.4 yrs, 65% male), 42 "non-DS mentally retarded" (non-DS MR) (mean age 30.9 ± 10.8 years, 57% male), 47 healthy controls (mean age 30.2 ± 11.5 years, 62% male)	Eyes-closed resting state, 12 channels, 10/20 system	Examined relative power using EEGs from 4 derivations in the left hemisphere (F3-A1, C3-A1, P3-A1, O1-A1). Five artifact-free 5.12 sec duration epochs recorded from O1 underwent FFT - used to analyse peak frequency of the occipital alpha rhythms (defined as the frequency with the most prominent peak in the 8-13 Hz band). Relative power in six bands were calculated in 4-30 Hz range (theta1 theta2, alpha1, alpha2, beta1, beta2)	Activities of daily life (ADL) assessed using a motor function subscale of the GBS scale (a rating scale for dementia syndromes). 21/40 DS individuals had non-contrast brain CT scans	Alpha peak frequency was significantly negatively correlated with age in DS group (linear decline, not true of both control groups) and was significantly lower in DS group compared to healthy controls and "non-DS MR" controls in age groups 35-44 and 45-54. Peak freq did not significantly correlate with GBS score and no associations of alpha frequency and basal ganglia calcification (n=5; measured by CT). Significant negative correlation found between alpha peak frequency and Sylvian fissure index (a measure of cortical atrophy in the temporal region). Relative power in YA DS compared to controls (15-24yrs): significant increases in theta1 and beta1 in all derivations and increase in beta2 frontally only; decrease in alpha2 in occipital, parietal and central. DS (25-34yrs) compared to controls: increase in alpha1 (parietal only), decrease in alpha2 all derivations, increase in beta1 (frontal and central only), increase in beta2 (all). Relative power in OA (DS compared to controls): increase in theta2 (all), increase in theta1 (parietal only), increase in alpha1 (occipital only),

							decrease in alpha2 (all). 45-54yrs increase in the theta and alpha1 (occipital only), decrease in alpha2 (all but frontal)
Age-related cognitive decline and electroencephalogram slowing in Down's syndrome as a model of Alzheimer's disease	Soininen, Partanen, Jousmaki, Helkala, Vanhanen, Majuri, Kaski, Hartikainen, Riekkinen	1993	DS (n=31, 17 male, mean age 35 ± 10 yrs); AD patients (n=69, 36 male, mean age 80.1 ± 9.5 yrs); Young controls (n=26, 14 male, mean age 26 ± 8 yrs); Elderly controls (n=16, 2 male, mean age 81.6 ± 7.1 yrs)	Eyes-closed resting state, 10 electrodes, 10/20 system, data from T6-O2 reported (temporo-occipital derivation). Four artefact-free epochs of 8.192 s recorded. FFT computed on a series of 12 half overlapping sections corresponding to 32.772 s of EEG signal	Computed absolute amplitude and power of fairly standard EEG bands (alpha 7.57 - 13.92 Hz) as well as peak frequency and mean frequency (for both whole spectrum and also combined alpha and theta = 4.15 - 13.92 Hz). A clinical neurophysiologist graded the EEG tracings blindly for various abnormalities (including slowing of the dominant occipital rhythm)	Examined cortical functions (using Luria's neuropsychological examination), automatic speech functions, speech understanding, word fluency, praxic functions, visual functions, memory	In DS there was a significant age-related decrease of peak frequency from 20 to 60 years (in both 4.15-13.92 and 1.46-20.02 Hz windows). Decrease in peak frequency significantly correlated with MMSE, visual, praxic, speech functions and list learning (this was similar to AD patients but not young or elderly controls). Alpha peak frequency in DS was 8.5 ± 2.3 Hz (compared to 5.9 ± 1.7 in AD, 9.6 ± 0.8 in YC, 9.3 ± 1.1 in EC). Power: There were no significant differences in absolute amplitude and power values between YA-DS (under 40, n=17) and OA-DS (40 and over, n=10)
Quantitative EEG study on premature aging in adult Down's syndrome	Murata T, Koshino Y, Omori M, Murata I, Nishio M, Horie T, Isaki K.	1994	32 DS (aged 20-46 yrs), 15 healthy young controls, 15 healthy OA controls (in their 60s)	16 electrodes, 10/20 system, eight 5-sec artefact-free epochs selected (providing 40 sec to be analysed)	Number of waves contained in 10 frequency bands (delta, theta1-3, alpha1-4, beta1-2) calculated using the "wave-form recognition method". Mean frequency of occipital region (O1) was also calculated in the theta-alpha band range	IQ: Koh's Block-design test, Goodenough's draw a man test	Mean frequency decreased with increasing age in DS (9.37 in 20s (n=15), 9.17 in 30s (n=9), 8.76 in 40s (n=8)). 20s and 40s groups were significantly different. In control group the mean frequency only decreased slightly with age (9.74 in 20s Vs 9.53 in 60s group) and this wasn't statistically significant. Also, DS group in 20s was significantly slower than controls in 20s. No correlations with frequency and IQ.

					(4-13Hz)		Compared to YA DS, OA DS have increased power in theta1 (occipital), theta3 (frontal and parietal), decreased power in alpha4 (diffuse areas) and decreased power in beta1 (diffuse areas). Compared to controls, OA controls have more theta2 power, more beta1&2 power, and less alpha2&3 power
EEG reactivity correlates with neuropsychological test scores in Down syndrome	Partanen, Soininen, Kononen, Kilpelainen, Helkala, Riekkinen.	1996	32 DS (age 21-60 yrs, mean age 35 yrs (SD 10yrs), 18 male); 31 age and gender matched controls (age 21-60, mean age 39yrs (SD 11yrs), 18 male)	10 channels, 10/20 system. Four artefact-free epochs of 8.192 s with eyes-open and again with eye-closed recorded. FFT computed on a series of 12 half overlapping 4.096 sections corresponding to a total length of 32.768 s of discontinuous EEG signal	Computed absolute amplitude and power of standard EEG bands as well as peak frequency and mean frequency. Reactivity: calculated EC/EO ratios for amplitude, power, % diminution of amplitude and power for all bands. A clinical neuropsychologist also graded the EEG tracings blindly for various abnormalities (including slowing of the dominant occipital rhythm)	Examined cortical functions (using Luria's neuropsychological examination), automatic speech functions, speech understanding, word fluency, praxic functions, visual functions, memory.	Individuals with DS showed mild slowing (n=12), moderate slowing (n=3), marked slowing (n=1). Amplitude of EC delta, theta and alpha and beta activity was increased in DS compared to controls. Both DS and controls had a significant reduction in EC alpha, beta and theta activity and decrease of EEG frequency with eye opening. EC/EO ratio in alpha band was significantly decreased in DS compared to controls, and all neuropsychological tests were significantly correlated with this (better ratio, better performance). Also found an inverse correlation in DS with EC/EO alpha ratio and age
Cognition-related EEG abnormalities in nondemented down syndrome subjects	Politoff, Stadter, Monson, Hass	1996	13 "non-demented" DS (mean age 33.8 yrs (SD 9.5yrs), 7 males); 13 normal age matched	21 channels, 10/20 system, eyes-closed resting state and flash stimulated EEG recordings. 28 artifact-free	O2-A2 electrodes used for analysis, alpha defined as 8-12.9 Hz. Dominant occipital freq	MMSE, picture absurdities test (PAT)	Amplitude of resting state activity was larger in DS than age-matched controls across whole spectrum but did not correlate with cognitive scores.

			control subjects (mean age 32.1 yrs (SD 8.4 yrs), 9 males)	epochs of 2.5 s covering 35.5 s with 51% overlapping was obtained for rest and for each flash intensity. Dirichlet window and FFT used for spectral analysis	(DOF) defined as frequency as the largest power peak in 2-20 Hz range in the T6-O2 channels. Measured absolute and relative power		Absolute power of delta, theta and beta was significantly larger in DS than controls. Relative power of all bands was not significantly different between DS and controls. However, DS had significantly larger absolute and relative power at the 4.5 and 8.8 Hz bins (bins are 0.39 Hz each). Power at 4.5 and 8.8 Hz bins also correlated significantly and negatively with both cognitive tests. DOF shift to the left in DS but not significantly different between groups and was not correlated to any tests. No significant correlations with age
Quantified electroencephalogram in adult patients with Down syndrome	Locatelli, Fornara, Medagliani, Akberoni, Franceschi, Rinaldi, Comola, Keocani, Canal, Comi	1996	33 YA DS (20-35 yrs), 12 OA DS (36-55 yrs), 20 YA healthy controls (age 20-35 yrs) and 20 OA healthy controls (age 36-55 yrs)	10 mins eyes-closed resting EEG, 21 electrodes, 10/20 system. FFT performed on at least 40 artefact-free epochs of 2.5 ms each	Examined relative and absolute power of delta, theta, alpha (8-11.9 Hz) and beta bands, and topographical distribution of each. Results were considered abnormal when they fell outside the mean normal values ± 2.5 SD	Neuropsychological test battery: abstract reasoning (Raven Colour Matrices; scores also transformed to give IQ score), language comprehension (Tolken Test), language production (verbal fluency), attention (Cancellation task) and memory (Rivermean Behavioural Memory	73% DS-YAs and 92% DS-OAs had abnormal EEGs. YAs and OAs showed increased power in delta (relative & absolute; centro-anterior regions), theta (absolute & relative; centro-posterior regions) and beta (absolute & relative; mostly parieto-temporal regions) and decrease in alpha. Decrease in alpha was statistically significant only in posterior regions in OA. When OA DS and YA DS compared, OAs only had a significant increase of theta power. DS participants overall had significantly slower alpha peak rhythm compared to controls (9.2 ± 1 Hz vs 9.7 ± 0.3 Hz). Alpha peak frequency did not correlate

						Test). Dementia assessed using criteria of Shapiro et al., 1993	with age in DS or in control groups. In DS, alpha peak frequency significantly correlated positively with with Raven Colour Matrices, Rivermean Behavioural Memory Test and Tolken Test scores. Severity of cognitive impairment affected prevalence of abnormalities - increasing severity was associated with decreased alpha power, increase of theta in posterior regions, and decrease of delta across scalp. Pattern was more pronounced in participants with dementia
P300 and EEG mapping in Down's syndrome	Medagliani, Locatelli, Fornara, Alberoni, Comola, Franceschi, Canal, Comi	1997	45 adults DS (16 M, mean age 30.6 yrs) subdivided into 33 YA (age 20-45) and 12 OA (36-56 yrs). Resting-state EEG healthy control subjects (20 YA (20-35) and 20 OA (36-55)) p300 healthy control subjects (30 YA (20-40) and 27 OA (21-60))	qEEG and auditory p300 mapping. 19 electrodes, 10/20 system, 10-mins eyes-closed rest recordings. FTT on at least 40 2.5s epochs. Auditory oddball ERP paradigm also recorded (details not provided here)	Resting-state analysis: Calculated relative and absolute power of delta, theta, alpha (8-11.9 Hz), beta examined. Topographic distribution of each band analysed through bidimensional maps with rectangular linear interpolation. Considered abnormal if fell outside control mean values ± 2.5 SD	Neuropsychological test battery exploring abstract reasoning (RCM), language comprehension (TT), production (VF), attention (CT), memory (RBMT). RCM scores were also transformed to give IQ. Dementia diagnosed based on clinical grounds (Shapiro et al. (1987) criteria) and cognitive test results	EEG "normal" in 10 and "abnormal" in 35 patients (73% of YA, 92% of OA). YA group: significant increase in delta power (75%), theta power (37%), beta power (37%), and 58% had significant decrease in alpha power. OA group: significant increase in delta power (54%), theta power (91%), beta power (36%), and 45% had sig decrease in alpha power. Topographically, significant increase of delta power in centro-anterior regions and parieto-temporal regions for beta power. In OA group, decrease in alpha power was statistically significant over posterior regions and there was a significant increase of absolute and relative theta

							power over centro-posterior regions. Cognitive impairment was accompanied by an alpha power decrease, theta increase (in posterior regions), delta increase (across scalp). This pattern was more pronounced in DS participants with dementia. DS without EEG abnormalities performed significantly better on most measures than those with abnormalities
On chronological changes in the basic EEG rhythm in persons with Down syndrome - with special reference to slowing of alpha waves	Katada, Hasegawa, Ohira, Kumagai, Harashima, Ozaki, Suzuki	2000	Cross-sectional: DS children and adults (n=265; range 8-55 years), non-DS "mental retardation" children and adults (n=242; 7-58 years), Healthy children and adults (n=239; 2-59 years). Longitudinal (period between 8-9 years): DS (n=28), non-DS "mental retardation" (n=14)	Recorded eyes-closed for 5-10 mins (to obtain at least 3 mins artifact-free), from six midline-sagittally arranged locations equally spaced along the scalp	3 second segments (n=20) were transformed to power spectra and averaged. Dominant frequency was decided from the peak of the mean spectrum. Analysis focused on frontal, central and occipital regions		Cross-sectional: In DS, alpha rhythm frequency lowered into 8 or 9 Hz in their 30s. Most maintained 8Hz frequency level after age 35. Longitudinal: Lowering took place in various of years of age individually, but an early distinct decrease was commonly noticed
Inter-hemispheric functional coupling of eyes-closed resting EEG rhythms in adolescents with Down syndrome	Babiloni, Albertini, Onorati, Vecchio, Buffo, Sarà, Condoluci, Pisto, Carducci, Rossini	2009	38 DS adolescents (18.7yrs ± .67 SE, 20 males), 17 age-matched normal controls (19.1yrs ± .39 SE). Additional analyses included data from 12	Eyes-closed resting EEG, 9 electrodes, 10/20 system, parents kept eyelids down if the participant could not, 5 minute recording, 256 Hz sampling rate, 2-sec artifact free epochs underwent	Power evaluated using FFT (Welch technique), interhemispheric directional EEG functional coupling evaluated using directed transfer function (DFT).	IQ using Weschler Intelligence scale for children Revised. For DS-MCI used various criteria (i.e. ICD-10) to diagnose this	Compared to controls DS had lower alpha1&2, beta1&2 and gamma power over larger regions but higher delta power in the frontal regions. Occipital EEG functional coupling: directionality in controls prevailed from right to left hemisphere. In DS directionality was

			DS with mild-cognitive impairment (MCI) (mean age 41yrs, 8 males) and 15 healthy controls (mean age 41.8yrs, 9 males)	spectral analysis	Standard bands including alpha1 (8-10.5 Hz) and alpha2 (10.5-13 Hz), beta1 and beta2		opposite (left to right). There were no correlations of directionality with IQ in DS. Further analysis revealed DS had greater inter-hemispheric functional coupling in central and temporal regions, whereas controls had greatest in frontal and occipital regions. Control analyses: MCI-DS had higher right-to-left inter-hemispheric directional functional coupling than old-controls
Cortical sources of EEG rhythms are abnormal in down syndrome	Babiloni C, Albertini G, Onorati P, Muratori C, Buffo P, Condoluci C, Sarà M, Pistoia F, Vecchio F, Rossini PM.	2010	45 DS subjects (mean age 22.8 yrs, 25 male), 45 age-matched cognitively normal subjects (mean age 22.4 yrs, 25 male)	5 mins eyes-closed resting EEG (parents kept eyelids down if the participant couldn't), 19 electrodes, 10/20 system, 256 Hz sampling rate, 2-sec artifact-free epochs (30 or more) underwent spectral analysis (epochs with blink artifacts were "corrected")	Alpha 1 (8-10.5 Hz) and alpha 2 (10.5-13 Hz) bands both analysed. Cortical EEG sources estimated using LORETA (compared relative power current source densities at cortical voxels) to overcome head volume conductor abnormalities. Alpha frequency calculated in extended range (as in Klimesch, 1999).	IQ: Weschler Intelligence scale for children Revised	DS alpha frequency was 10.1 Hz ± .2 SEM, control was 9.6 Hz ± .1 SEM. This difference was not statistically significant. EEG cortical sources of alpha and beta were lower in amp in DS than controls (central, parietal, occipital, temporal areas), higher amplitude for delta sources (occipital only)
Cognitive impairment and EEG background activity in adults with Down syndrome: A topographic study	Velikova, Magnani, Arcari, Falautano, Franceschi, Comi, Leocani	2011	25 adults with DS (mean age 38 yrs, range 30 - 69 yrs, 6 male), 25 age and gender matched controls (mean age 36	5 mins eyes-closed resting EEG, 29 channel electrode cap, 10/20 system	Artifact-free 2-sec epochs (at least 70 per subject) underwent FFT. Average absolute power for each channel was computed in 1-30 Hz	Neuropsychological test battery (MMSE, Wechsler Adult Intelligence Scale, Attentive Matrices Test, Digit Span test,	Alpha frequency was significantly lower in DS compared to controls. WAIS-total and MMSE correlated positively with alpha frequency in DS. WAIS and RBM were negatively correlated with occipital alpha power. Absolute power

			<p>yrs, range 28 - 65 yrs)</p>	<p>with 1Hz steps. Percent power was calculated as % value of a 1Hz segment. Alpha frequency was the freq with maximum power within the alpha band over occipital electrodes (O1 and O2). Absolute and relative power for traditional bands (alpha1&2 and beta1-3 used) and absolute power of individually adjusted bands for theta and alpha 1-3. Also did source localisation using e/sLORETA</p>	<p>Rivermead Behavioural Memory, Short story recall, Raven's Coloured Progressive Matrices, Tolken test, Semantic verbal fluency, Geometric shape copy</p>	<p>in fixed bands: Compared to controls DS had significantly higher absolute power and significantly increased CSD in theta, alpha1 and beta1. WAIS correlated negatively with CSDs in right frontal lobe and right PCC. RBM correlated negatively with CSD in right BA9. Negative correlation was found between absolute occipital power and cognitive test performance (using 1Hz bands). Absolute power in IAF-adjusted bands: maximum alpha power was in upper alpha band for control group and max in DS was in the lower alpha2 band. Significantly increased CSD in all individually adjusted bands was seen in DS compared to controls. WAIS correlated negatively with CSD in right BA9 (in theta band). Compared to controls DS had sig higher absolute power in theta and alpha bands. Relative power: Max value of alpha was found in alpha1 in DS and alpha2 in controls. Significant difference found between groups in alpha2 - decreased CSD in cingulate cortex in DS (no correlations though found between regions of decreased CSD in alpha2 and cognitive scores). Average value for relative alpha2 and its occipital values</p>
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							correlated with cognitive scores (negative correlation with power at 7-8Hz and positive correlation at 11-12Hz)
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Table 2.1 Summary of studies in literature review

A summary of details provided by each identified paper within the literature review of this thesis that met criteria for inclusion (n=13; ordered by chronological year of publication). Many publications did not provide detailed descriptions of EEG protocols, analyses or results; this reflected in a lack of detail within this table for such studies. Where information was provided by authors it has been included.

2.4.2 Resting-state EEG characteristics associated with DS

This section will discuss differences in EEG reported between adults with DS compared to TD control subjects (chronologically age-matched unless stated otherwise) and group differences within the population with DS (i.e. younger vs older adults). Power measures will first be discussed, followed by frequency measures, and finally any other EEG characteristics reported by the identified studies. All findings related to cognition and cognitive decline will be discussed in the following section (“2.4.3 Resting-state EEG characteristics associated with cognition in DS”).

2.4.2.1 Power measures associated with DS

Alpha power

Individuals with DS compared to controls

Differences in alpha power are commonly reported in individuals with DS compared to chronologically age-matched control subjects of the TD population. However studies report conflicting results, including decreased alpha power (Babiloni et al. 2009, Locatelli et al. 1996, Medaglini et al. 1997), increased alpha power (Partanen et al. 1996), and no significant differences in alpha power (Politoff et al. 1996).

It is possible that differences in alpha power between individuals with DS and individuals from the TD population may only become apparent with age. In line with this, two studies have reported a significant decrease in alpha power relative to TD controls in older adults with DS (aged 36 and over) that was not significant in younger adults (aged 20-35) (Locatelli et al. 1996; Medaglini et al. 1997). Age may therefore be a potential contributor to conflicting results between studies, however it has been previously noted these two studies are likely to be from the same sample, and therefore Medaglini et al. (1997) should not be considered a replication of this finding.

Interestingly, some studies have split the alpha band into lower-alpha and upper-alpha (typically 8-10 Hz and 10-13 Hz respectively). These studies report an increase in lower-alpha power with a concurrent decreased upper-alpha power in adults with DS compared to TD controls (Ono 1993, Velikova et al. 2011). Therefore within the alpha band itself, power differences in opposing directions may exist between individuals with DS relative to TD controls. As such, differences relative to controls may cancel each

other out when overall power within the alpha band is examined. This may also therefore be a source of conflicting results between studies.

Furthermore, Ono (1993) found topographical differences in alpha power for the different participant age groups investigated; the increase in lower-alpha power occurred over the parietal cortex for young adults with DS (aged 25-34) but over the occipital cortex for older adults with DS (aged 35-54). In contrast, decreases in upper-alpha power were more widespread for both age groups. Topographical differences in alpha power may therefore exist across age groups for individuals with DS relative to TD controls, and may be an additional source of conflicting results between studies.

Taken together, these studies suggest alpha atypicalities in DS may be common, but more research is needed to fully elucidate these differences. It is possible that individuals with DS have more lower-alpha activity and less upper-alpha activity compared to TD controls (i.e. slower alpha). Differences may become accentuated (or only appear) with increasing age, and may also differ in location across the scalp. Longitudinal studies are necessary to fully examine age-related changes in alpha power as other factors (e.g. cohort effect) may have influenced the cross-sectional results detailed here.

Within DS subgroup analysis of alpha power

Three of the identified studies have examined differences in alpha power between younger and older individuals with DS. Soininen et al. (1993) reported no significant differences in alpha power (defined as 7.6-13.9 Hz) over the temporo-occipital derivation between individuals with DS below age 40 (n=17) and those age 40 and over (n=10). Locatelli et al. (1996) also reported no significant differences in alpha power (defined as 8-11.9 Hz) across various regions of the scalp between younger (age 20-35 yrs; n=33) and older (age 36-55 yrs; n=12) individuals with DS.

In contrast, Murata et al. (1994) reported an age-related power decrease in upper-alpha (defined as 11-13 Hz) across diffuse areas when comparing individuals with DS in their 20s (n=15) to individuals in their 40s (n=8). It may be that age-related differences in alpha power were apparent to Murata et al. due to the use of several smaller alpha frequency bands (four in total), whereas the two studies reporting no significant findings each used one large alpha band. Additionally, Locatelli et al. only examined alpha activity up to 11.9 Hz, and therefore may not have used a high enough cut-off to observe significant upper-alpha differences. Overall findings of Murata et al.

(1994) are in accordance with findings comparing individuals with DS to TD controls in the previous section, where it was suggested that reduced upper-alpha activity compared to TD controls may become accentuated with increasing age. However, as this within-DS finding is from single cross-sectional study, additional research is necessary to investigate this further.

Power measures in other bands

Individuals with DS compared to controls

Increases in power-related measures in all other power bands (delta, theta, beta and gamma) are commonly reported for adults with DS compared to chronologically age-matched TD control subjects (Babiloni et al. 2009, Babiloni et al. 2010, Locatelli et al. 1996, Medaglini et al. 1997, Murata et al. 1994, Ono 1993, Partanen et al. 1996, Politoff et al. 1996, Velikova et al. 2011). However, for beta and gamma power, Babiloni et al. (2009, 2010) reported reduced power relative to TD controls. Reasons for this inconsistency are unclear but it is worth reiterating that Babiloni et al. (2009, 2010) held down the eyelids of participants who were unable to close their eyes themselves during recording. In this case increased sensory stimulation could influence beta power (beta activity has been linked to somatosensory processes, as mentioned previously), and gamma activity has been linked to worry (Oathes et al., 2008), which could have been higher in participants undergoing this protocol.

Overall for slow wave frequencies (i.e. delta and theta), findings from topographical analyses report individuals with DS may show increases in delta power, particularly in frontal and centro-anterior regions (Babiloni et al. 2009, Locatelli et al. 1996, Medaglini et al. 1997), and increases in theta power, particularly in centro-posterior regions (Locatelli et al. 1996, Medaglini et al. 1997) relative to TD controls. Interestingly, increases in lower-theta (4-6 Hz) power may be widespread in young adulthood (age 15-24) but become localized, in particular over parietal regions, by mid-adulthood (age 35-44) (Ono 1993). This further emphasises the need to consider age-related and topographical differences in EEG power between individuals with DS relative to TD controls.

Overall for faster frequencies (i.e. beta and gamma), findings from topographical analyses report beta power may be particularly increased in parieto-temporal regions in individuals with DS relative to TD controls (Locatelli et al. 1996, Medaglini et al. 1997). When beta is subdivided into lower and upper beta (13-20 Hz and 20-30 Hz

respectively) and examined across age-groups, in young adulthood (age 15-24) increases in lower-beta power may be widespread across the scalp while increases in upper-beta power are confined to frontal regions. Once the brain is fully developed in adults aged 25-34, the increases in lower-beta power may become confined to frontal and central regions while increases in upper-beta power become more widespread (Ono 1993). Although it has been suggested that such age-related changes may correspond to brain maturation, these findings are based upon a single cross-sectional study (Ono et al., 1993), and so definitive conclusions cannot be made; longitudinal designs are required to enable age-related changes to be accurately investigated in this population.

Overall these studies suggest that individuals with DS may have more power in both slow (delta and theta) and fast (beta and gamma) frequency bands compared to TD control subjects, with the extent and location of such differences likely to vary with age (i.e. upper-beta oscillations may become more widespread while lower-theta activity may become more localised).

Within DS subgroup analysis

The above findings pertain to individuals with DS compared to chronologically age-matched TD control subjects. As previously mentioned, three of the studies identified in this literature review have examined power differences between individuals with DS. Soininen et al. (1993) reported no significant differences in EEG power in any frequency bands between individuals with DS below age 40 and those age 40 and over. In contrast, Murata et al. (1994) reported an age-related increase in theta power with a concurrent power decrease in upper-alpha and lower-beta activity. Locatelli et al. (1996) also reported an significant age-related increase in theta power.

A possible reason for inconsistencies between these three studies is Soininen et al. (1993) only examined temporo-occipital electrodes whereas the other two studies examined activity across the scalp. This is particularly important as Murata et al. (1994) reported upper-theta power was increased only in frontal and parietal regions; such differences would therefore not have been apparent for Soininen et al. (1993).

Taken together these findings suggest that in DS an age-related increase in slow-wave (theta) and decrease in medium-fast waves (upper-alpha to lower-beta range) may occur, which is indicative of an age-related slowing of the EEG spectrum.

2.4.2.2 Frequency measures associated with DS

Individuals with DS compared to controls

Studies examining differences in alpha peak frequency between individuals with DS compared to TD controls are inconsistent. Some studies have reported a slower frequency in DS (Ono et al. 1992; Soininen et al. 1993; Murata et al. 1994; Locatelli et al. 1996; Katada et al., 2000; Velikova et al. 2011) whereas others report no significant difference (Politoff et al. 1996; Babiloni et al. 2010). It should be noted, however, that Politoff et al. (1996) measured peak frequency across a 2-20 Hz range and Babiloni et al. (2010) had eyelids of participants held down; such differences make comparison to studies adopting more conventional methodology problematic.

Studies reporting a significant difference in alpha peak frequency typically report this value as lying below 9 Hz in individuals with DS. In contrast to this, mean alpha peak frequency is considered to be around 10 Hz in the TD population (Klimesch, 2012). Furthermore data from these studies indicate that some individuals with DS have an alpha peak that falls within what is typically considered to be the theta range (i.e. 4-8 Hz) (e.g. Soininen et al., 1993; mean alpha peak frequency 8.5 ± 2.3 Hz). Extended alpha approaches may therefore be appropriate for the analysis of peak characteristics in individuals with DS.

At present it is unclear if the overall reported slower alpha peak in individuals with DS compared to TD controls discussed here is found throughout the lifespan or whether instead it is an age-related change. Perhaps the most detailed analysis of this issue is provided by the large cross-sectional (and longitudinal) study by Katada et al. (2000), in which 265 individuals with DS ranging from 8 to 55 yrs old were compared to 239 chronologically age-matched TD controls. The longitudinal arm of the study is discussed in the section below. From the cross-sectional arm of the study, Katada et al. reported there was no difference in alpha peak frequency in individuals with DS before age 20 compared to TD controls, however a slower alpha peak in individuals with DS became apparent after this age. Overall Katada et al. reported slowing of the alpha peak occurred earlier in individuals with DS compared to TD controls, and slowing in DS was also more prominent (i.e. substantial slowing in the thirties was noted in individuals with DS but did not occur until the fifties in TD controls). These findings suggest slower alpha peak frequency in individuals with DS is not present throughout the lifespan but may instead be a result of age-related changes.

Within DS subgroup analyses of EEG frequency

In accordance with findings comparing individuals with DS to TD controls, studies analysing the relationship between alpha peak frequency and ageing within adults with in DS consistently report that slowing increases with age (Katada et al. 2000; Murata et al. 1994; Ono et al. 1992, 1993; Soininen et al. 1993). However, one study failed to find a significant relationship between alpha peak frequency and age (Locatelli et al., 1996). This was a cross-sectional study and the authors noted the lack of significant findings was possibly due to high inter-individual variability in this measure. In contrast, Katada et al. (2000) employed a longitudinal design, with change in frequency within individuals monitored over time (around 8 years) and shown to decrease substantially.

The age at which slowing is reported to take place varies substantially between studies, indicating the individual age at which this takes place may be highly variable. It is also possible methodological differences between studies – in terms of age brackets used in cross-sectional studies – contribute to differences in the estimated age of slowing. For instance the longitudinal study by Katada et al. (2000) reported this occurred substantially in individuals in their thirties (n=28). In contrast, cross-sectional studies give broader estimates, including between 20-60 years (n=31; Soininen et al. 1993) and between 20-40 years (n=32; Murata et al. 1994).

Due to large variability in these estimates it is difficult to determine whether slowing is related to brain maturation (as indicated by early changes), ageing (as indicated by later changes), or whether slowing occurs throughout adulthood in DS. Large longitudinal studies are necessary to elucidate this further. Topographical differences are also important to consider, as Katada et al. (2000) examined slowing in several different brain regions (frontal, central and occipital), and observed slowing slightly earlier in frontal and central areas than in occipital regions.

2.4.2.3 Other resting-state EEG characteristics associated with DS

In the studies identified by this review, two further EEG characteristics have been investigated in individuals with DS: eyes-open/eyes-closed ratio (Partanen et al., 1996) and inter-hemispheric connectivity (Babiloni et al., 2009).

As previously mentioned in section “2.2. Resting-state EEG”, alpha activity is suppressed when the eyes are open compared to when the eyes are closed. Partanen et al. (1996) examined this process in individuals with DS by comparing EO and EC

EEG recordings. Partanen et al. (1996) reported the ratio of alpha activity between the two conditions was significantly lower in individuals with DS (n=32) compared to chronologically age-matched TD controls (n=31). This indicates there is less of a change in alpha activity in response to eye-opening in individuals with DS compared to TD controls. Partanen et al. also examined this ratio within individuals with DS and reported it was inversely correlated with age (M = 35 yrs; SD = 10 yrs; range 21-60 yrs). As the ratio of alpha activity between these two conditions is thought to reflect level of resting-state arousal (Barry & De Blasio, 2017), reductions in this measure in individuals with DS is suggestive of an altered state of alertness, that additionally may decrease further with age (although longitudinal studies are necessary to confirm this).

Finally, Babiloni et al. (2009) examined inter-hemispheric connectivity (using a method for examining the direction of information flux between hemispheres) and found while this was greatest in frontal and occipital regions in chronologically age-matched TD control subjects (n=17), in individuals with DS (n=38) it was greatest in central and temporal regions. Furthermore, when the direction of functional coupling was examined, this prevailed from right-to-left hemisphere in controls and from left-to-right in individuals with DS. At present the implications of this are unclear. Overall these findings are indicative of atypical connectivity patterns in individuals with DS, however as this is a single study more research is needed to replicate these findings.

2.4.2.4 Summary of resting-state EEG characteristics associated with DS

Research suggests there are resting-state characteristics across the EEG spectrum that are associated with DS. Overall it appears that DS is associated with increased power in both slow and fast frequencies, however upper-alpha activity (around 10-13 Hz) may be decreased. In line with this, analyses of alpha frequency indicate alpha rhythms are slower in individuals with DS. Atypical connectivity patterns and altered EO/EC ratio may also be associated with DS, but further research is necessary to investigate this.

Regarding age related changes, studies comparing individuals with DS to TD controls and studies comparing EEG activity between younger and older adults with DS in general indicate the same findings. Multiple measures (including both power and frequency) are indicative of age-related slowing of the EEG spectrum (particularly in the alpha band) in individuals with DS. Such age-related slowing is associated with a high degree of inter-individual variability in terms of age of onset, but is likely to occur substantially in individuals' thirties. Interestingly this is around the time increasing AD

neuropathology is known to occur in DS (see section “1.2 Neurobiological features of Down syndrome”).

These findings are in accordance with the hypothesis that a “slow wave brain” is a major characteristic of DS (Babiloni et al., 2009), and suggest this particular characteristic may become accentuated with age and/or increasing neuropathology.

2.4.3 Resting-state EEG characteristics associated with cognition in DS

This section discusses studies investigating correlations between resting-state EEG characteristics and cognition in individuals with DS. EEG characteristics associated with cognitive ability will first be discussed, followed by characteristics that have been associated with cognitive decline.

2.4.3.1 Resting-state EEG characteristics associated with cognitive ability

Alpha peak frequency

Five of the studies identified investigated the relationship between alpha peak frequency and cognition in individuals with DS. Three of these studies report a significant positive correlation between alpha peak frequency and ability (Soininen et al., 1993; Locatelli et al., 1996; Velikova et al., 2011), and two report non-significant findings (Ono et al., 1993; Politoff et al., 1996).

Findings from studies controlling for decline

Only two of these five studies identified (Locatelli et al., 1996; Politoff et al., 1996) ensured that participants did not have evidence of significant cognitive decline or dementia (as determined by clinical assessment). It can therefore be concluded that only the findings of these two studies are not confounded by significant detectable decline. Of these two studies, Locatelli et al. (1996) reported a significant positive correlation of alpha peak frequency (8-12 Hz) across a range of cognitive domains, including abstract reasoning abilities (measured by Raven Colour Matrices), memory (Riverman Behavioural Memory test) and language comprehension (Tolken test scores). This was a relatively large study (n=45; age range 20-56; mean age 30.6 yrs). In contrast, the relatively small study by Politoff et al. (n=13) did not find a significant relationship between peak frequency and cognitive ability.

In this study (Politoff et al., 1996), the Picture Absurdities Test (PAT) and the Mini-Mental State Examination (MMSE) score were used to assess cognitive ability. The PAT is a non-verbal measure of intelligence. The MMSE is a questionnaire designed to test for the presence of cognitive impairment within in the TD population, which is questionable as a tool for measuring cognitive ability in individuals with DS. Furthermore Politoff et al. (1996) focused their recruitment on “highly functional subjects”. Consequently this study is likely to have a smaller range of cognitive ability than Locatelli et al. (1996). This may have reduced the ability of the study to link cognitive ability with EEG measures. Finally it is worth noting that Politoff et al. (1996) measured peak frequency across the 2-20 Hz window (as opposed to within the alpha frequency band) which is an additional potential source of inconsistency. As discussed in the previous section, alpha peak frequency did not correlate with age in either of these two studies.

Findings from studies not controlling for decline

Of the three studies not controlling for the possible presence of significant cognitive decline or dementia, two of these studies reported a significant positive correlation of alpha peak frequency and cognitive ability (Soininen et al., 1993; Velikova et al., 2011), and one reported no significant correlation (Ono et al., 1993). However, Ono et al. (1993) can be criticised on the grounds that the only measure of cognitive ability used was a motor function subscale of a rating tool for dementia within the TD population (Gottfries- Bråne-Steen (GBS) Scale; Gottfries et al., 1982). This was used by the authors to provide an estimate of Activities of Daily Life. The choice of this tool to measure cognitive ability in individuals with DS is questionable. Although this is a relatively large study (n=40; mean age 30.3 yrs; range 16-54 yrs), results are not comparable with studies using more appropriate tests of cognitive ability. As discussed in the previous section, Soininen et al. (1993) and Ono et al. (1993) reported a significant negative correlation between alpha peak frequency and age. Velikova et al. (2011) did not analyse the relationship between alpha peak frequency and age within adults with DS.

The two studies reporting a significant positive correlation between alpha peak frequency and cognitive ability (that did not control for decline) reported this EEG measure was significantly positively correlated with a range of cognitive measures. This included general cognitive ability (measured by WAIS-total; see previous section

“1.3.3 Cognitive testing in DS”; Velikova et al., 2011), visual and speech functions, praxic functions and list learning (Soininen et al., 1993).

Alpha peak frequency summary

Together these studies are indicative of a positive relationship between alpha peak frequency and cognitive ability in individuals with DS, however due to potential issues controlling for cognitive decline further research is warranted. At present only one out of two studies controlling for cognitive decline has reported a significant association with alpha peak frequency and cognitive ability. Age is also a potential confounder in the relationship between alpha peak frequency and cognitive ability. Two of the five studies identified here reported a significant negative correlation between age and alpha peak frequency but did not attempt to control for this relationship in the analysis between alpha peak frequency and cognitive tests scores.

Power measures

Three of the identified studies in this review have examined the relationship between power and cognitive ability. Two attempted to control for cognitive decline and one did not. None of the three studies attempted to control for any potentially confounding influence of age on the relationship between power and cognitive ability.

Findings from studies controlling for decline

Two of these studies controlled for the presence of significant cognitive decline by either excluding individuals with evidence of decline from the study (Politoff et al., 1996) or by analysing these individuals separately to individuals without detectable decline (Medaglini et al., 1997) using clinical assessment criteria. Politoff et al. (n=13) reported a significant negative correlation between power at 4.5 (theta) and 8.8 Hz (lower-alpha) frequency bins and cognitive test ability (using the PAT). This study, however, is restricted to higher functioning participants and may therefore be not generalisable across those with DS.

Medaglini et al. (1997) reported that increased slow wave power (delta and theta) and reduced alpha power (8-12 Hz) was accompanied by attention and memory deficits (Cancellation Task and Rivermead Behavioural Memory Task respectively). This relationship was found in participants with and without dementia, but was reported as

being more apparent in those with dementia (n= 4) than without (n=41) (discussed in more detail in the section on cognitive decline below). The findings of this study indicate a negative correlation between slow wave power and cognitive test scores, similar to the findings of Politoff et al. (1996). It appears that findings relating to alpha activity, however, are inconsistent between these two studies. Differences in cognitive ability between studies and also methodological differences may be potential sources of this. For example, Medaglini et al. (1997) measured alpha power across 8-12 Hz whereas Politoff et al. (1996) used frequency bins of 0.4 Hz.

Findings from studies not controlling for decline

Although Velikova et al. (2011; n=25) did not attempt to control for the presence of cognitive decline or dementia, this study also reported a negative correlation between cognitive scores (measured using WAIS and RBM) and theta power (7-8 Hz frequency bin).

Power measures summary

Together the findings of studies analysing the relationship between power and cognitive ability in DS are in accordance with alpha frequency analyses in the above section, which associated slower activity with worse cognitive performance. It is of particular interest that slowing of the EEG – indicated as a characteristic feature of DS by studies discussed in section “2.4.2.1 Power measures associated with DS” – is associated with lower cognitive ability.

However, only two of the studies identified here attempted to control for the potential presence of cognitive decline, and none attempted to control for any potentially confounding influence of age. Furthermore, methodological differences between studies make comparison problematic. More research is required to fully elucidate the relationship between EEG power measures and cognitive ability in individuals with DS.

Eyes open/ eyes closed (EO/EC) alpha ratio

A further investigated EEG characteristic in relation to cognitive ability in individuals with DS is the EO/EC alpha ratio, examined by one study identified in this review. Partanen et al. (1996) reported this ratio was significantly positively associated with all neuropsychological measures investigated (including automatic speech, understanding

of speech, word fluency, visual functions, praxis functions, and list learning). It was discussed in section “2.4.2.3 Other resting-state EEG characteristics associated with DS” that this ratio is reduced in individuals with DS (n=32) relative to chronologically age-matched TD controls (Partanen et al., 1996). It therefore appears that individuals with DS with an EO/EC ratio closer to TD-levels show better performance on a range of cognitive tasks. This adds further evidence to the association between atypical alpha activity and impaired cognitive ability in DS. However, this study did not control for any potentially confounding influence of cognitive decline or age. This is particularly important because the EO/EC alpha ratio was shown to further reduce with age in individuals with DS in this study.

2.4.3.2 Resting-state EEG characteristics associated with cognitive decline in DS

Two of the identified studies in this review have examined the relationship between resting-state EEG characteristics and cognitive decline (or diagnosis of dementia) in individuals with DS. It has been previously noted, however, these studies are by the same group published one year apart, and appear to report the same participant demographics and EEG methodology – indicating that participants may be of the same sample (Locatelli et al., 1996; Medaglini et al., 1997).

These studies both report a significant decrease in alpha power (8-12 Hz) with a concurrent increase in the power of theta (4-8 Hz) and delta (0.4-4 Hz) in individuals with DS with dementia (n=4; defined according to clinical assessment criteria) compared to those without dementia (n=41). This a pattern suggestive of EEG slowing, however the sample size of individuals with dementia is particularly small.

Finally, Devinsky et al. (1990) was excluded from this overall literature review of EEG in DS on the grounds that EEG analysis was restricted to clinical interpretation, however results of Positron Emission Tomography (PET) and Computerised Tomography (CT) scans utilised by this study are relevant to this particular section and therefore are worth mentioning. The results of these scans suggested that, compared to chronologically age-matched TD controls, younger adults with DS (aged 19-37) with atypical alpha activity (upon clinical EEG interpretation) had specific areas of increased cerebral glucose metabolism, whereas older adults with DS (aged 42-66) with atypical alpha activity had notably reduced overall cerebral glucose utilisation and parietal hypometabolism. The results of cognitive tests revealed that younger adults with atypical alpha activity did not have reduced cognitive ability when compared to younger

adults with DS with typical alpha activity, but in older adults atypical alpha activity corresponded to a clinical diagnosis of dementia (n=4).

This study is important in demonstrating that neurobiological mechanisms underlying atypical alpha activity may vary with age – in younger adults atypical alpha activity did not correspond to reduced cognitive ability but cerebral metabolic activity was increased in specific areas, whereas in older adults alpha atypicalities corresponded to decline in both cognitive and metabolic function. Devinsky et al. (1990) suggest that the mechanisms underlying atypical alpha activity in DS may be AD-related neuropathological changes in older adults and in younger adults may be related to cerebral immaturity. However, considering the small sample (n=28) further studies are needed to assess this hypothesis further.

2.4.4 Summary and implications

Research investigating resting-state activity in DS spans many decades and so methodological approaches vary considerably, making direct comparisons between studies often problematic. Lack of detailed methodological reporting (e.g. whether paradigms were EO or EC) is also an important issue.

It appears that differences between individuals with DS and TD controls exist across the EEG spectrum but are particularly apparent in the alpha band, where both power and frequency measures suggest there is an overall slowing of these oscillations in DS and that this becomes further accentuated with age. The age at which substantial slowing takes place appears highly variable but is likely to occur alongside, if not immediately preceding, neuropathological changes associated with AD.

Interestingly, evidence suggests alpha slowing in individuals with DS may be a characteristic that is particularly associated with cognitive ability (with markers indicative of slowing associated with worse performance), and may also be a potential marker of decline in this population. At present it is unclear whether associations between slowing and ability are a consequence of issues controlling for age and decline within studies, or whether such markers of slowing are in fact biomarkers of ability that are additionally sensitive to AD-related changes.

Methodological implications of this review that are relevant to this thesis include not to consider classical EEG frequency bands as set parameters, with analysis appearing to benefit from split-band (e.g. lower-alpha and upper-alpha) and combined-band (e.g.

theta-alpha) approaches in this population. Examining the topographical distribution of signals also appears to yield subtle differences that may not otherwise be apparent. Furthermore obtaining both EO and EC data from participants allows the investigation of differences between these conditions which may prove useful. It also is vital that studies examining the relationship between EEG characteristics and ability attempt to control for the potentially confounding influences of age and presence of dementia and/or cognitive decline.

2.5 Thesis aims and hypotheses

2.5.1 Aims

The overarching aim of this thesis is to identify resting-state EEG measures (obtained from EO and EC paradigms) that are predictive of general cognitive ability in adults with DS. The influence of age on resting-state EEG measures will also be identified, and it will be determined whether age is additionally influencing any relationships between EEG measures and general cognitive ability. EEG measures to be explored include power, frequency and EO/EC ratio (i.e. reactivity). In addition to this, cortical circuitry underlying EEG oscillations of interest (i.e. those predictive of general cognitive ability) will be inferred using dynamic causal modelling (DCM), with the aim of offering potential mechanistic insights underlying these relationships.

Elucidating factors underlying individual differences in general cognitive ability in adults with DS is important for furthering our understanding of cognition in DS. This is not only important in its own right (e.g. to identify potential targets for cognitive enhancement in individuals with DS and/or biomarkers for clinical trials), but is also a first necessary step in order to identify and understand later changes associated with cognitive decline in this population.

In particular, enhancing cognitive ability in individuals with DS may be achievable through understanding factors underlying individual differences in cognition, and from this identifying potential targets for cognitive enhancement. Underlying this premise is that abilities vary greatly between individuals with DS, despite all individuals having an extra copy of chromosome 21. For example, some individuals with DS have IQ above what is considered an ID (IQ > 70). It is therefore possible that a level of cognitive functioning close to TD levels can occur in the presence of an additional chromosome 21, while others are much more severely affected.

There are four primary aims of the thesis, which correspond to four experimental chapters. Additional secondary aims are detailed within each chapter. The four primary aims of this thesis are:

- i) To investigate the feasibility and generalisability of EO and EC resting-state EEG recordings in adults with DS (chapter 4);
- ii) To identify differences in EC resting-state EEG activity between adults with DS (with no evidence of cognitive decline or diagnosis of dementia) and TD age- and sex- matched control subjects (chapter 5);
- iii) To investigate how EEG spectral measures obtained during EO and EC resting-state recordings are related to age and general cognitive ability in adults with DS (with no evidence of cognitive decline or diagnosis of dementia) (chapter 6);
- iv) To investigate potential cortical circuitry underlying EEG oscillations of interest (identified in chapter 5) using DCM (chapter 7)

2.5.2 Hypotheses

The following hypotheses will be tested, corresponding to the primary aims detailed above:

- i) Individuals with DS will have less power in the alpha band but more power in other EEG bands compared to TD age- and sex- matched control subjects;
- ii) Measures indicative of EEG slowing and reduced reactivity will be associated with increasing age and lower general cognitive ability. Significant associations with general cognitive ability are expected for EC measures only;
- iii) Cortical circuitry underlying EEG oscillations of interest in adults with DS, when modelled using DCM, will show an inverse relationship between inhibition and general cognitive ability.

Chapter 3 General Methods

3.1 Overall study design

The study is nested within a larger project investigating cognitive abilities and cognitive decline in a large cohort of adults with DS. This larger project is one stream of a multidisciplinary consortium project called the London Down Syndrome Consortium (LonDownS) focused on variability in the AD phenotype in adults with DS. Some methodological decisions were undertaken in the wider context of this multidisciplinary group. For example, in order to align these adult experiments with infant protocols it was necessary to include an EO resting-state recording paradigm during which participants were shown a cartoon.

The study reported in this thesis has a cross-sectional design which involved participants taking part in two separate experimental sessions. The first session consisted of a cognitive assessment (LonDownS cognitive test battery; Startin et al., 2016; see appendix) which took place either in the participant's own home or at a suitable location of their choosing (e.g. local day centre). The second session consisted of the EEG recording session at the Institute of Child Health (ICH) in London. Efforts were made to keep the number of days between sessions to a minimum, however a large degree of flexibility was necessary in order to achieve maximum participation. The length of time between sessions was kept to a minimum for older adults (aged 36 years and over) where possible ($n = 36$, mean = 91.17 days (61.44 SD), median = 70.00, range 0 - 265 days), as cognitive decline between sessions was more likely. A greater period between sessions was allowed for younger adults (aged 16-35 years) to maximise recruitment ($n = 52$, mean = 138.63 days (126.29 SD), median = 99.50, range 0 - 716 days), as cognitive decline between studies was not expected.

3.2 Ethical considerations

Ethical approval was obtained for the study from the North Wales West Research Ethics Committee (13/WA/0194). Where individuals had capacity to consent for themselves written informed consent was obtained. Where individuals did not have capacity to consent for themselves a consultee was appointed and asked to sign a form to indicate their decision regarding the individuals' inclusion based on their

knowledge of the individual and his/her wishes, in accordance with the UK Mental Capacity Act 2005. All participant information related to the study (including information sheets and consent forms) was written in easy-read format (see appendix). This was in order to support individuals to make their own decision in accordance with the UK Mental Capacity Act 2005.

3.3 Participant recruitment

3.3.1 Cognitive assessment

Participants were recruited for session 1 (LonDownS cognitive assessment) across England and Wales (focusing on the Greater London area and South East England) via local care homes, DS support groups and existing participant databases. We also established a network of National Health Service (NHS) Trust sites to identify and approach potential participants. Participants were given a gift voucher as compensation for their time and all travel expenses were reimbursed.

To be included in the study participants were required to be aged 16 and over and have a clinical diagnosis of DS (n=315). This was confirmed genetically using saliva or blood samples. Participants were excluded where genetic testing revealed no additional chromosome 21, mosaicism or translocation (n=2). Participants with a clinical diagnosis of dementia were included (n=51). Participants with an acute physical or mental health condition were, however, excluded (although when such participants recovered they regained eligibility for the study). Participants had the right to withdraw and one individual did so after beginning the assessment.

The following is an explicit list of inclusion criteria for the cognitive assessment stage of the study:

- Participant has a clinical diagnosis of DS
- Participant is aged 16 and over
- Participant does not have an acute physical or mental health condition

3.3.2 EEG assessment

Participants for session 2 (EEG assessment) were recruited from the LonDownS participant pool of adults (detailed above). Individuals from the LonDownS database who were within a day's return travelling distance of London were invited to take part. Individuals were only invited if it was felt they would be suitable for EEG in terms of being able to tolerate wearing an EEG cap for up to an hour. This was based on discussions with participants, parents and/or carers. Participants with a clinical diagnosis of dementia were included at this stage but were later excluded for specific EEG analyses (Chapters 5, 6 and 7). Further exclusion criteria was also applied for specific analyses (detailed within each chapter).

The following is an explicit list of inclusion criteria for the EEG assessment stage of the study:

- Participant has taken part in session 1 (cognitive testing session)
- Participant does not have an acute physical or mental health condition
- Participant lives within a day's return travelling distance of London
- Participant may to tolerate wearing an EEG cap (based on discussions with participants, parents and/or carers)
- participants had adequate hearing and vision (assessed during the initial cognitive session)

3.4 Cognitive assessment

Cognitive testing consisted of the LonDownS cognitive test battery (Startin et al., 2016; see appendix). This included both cognitive tests and informant questionnaires to assess general abilities, memory, executive function, and motor coordination abilities in adults with DS. This thesis is concerned only with general cognitive ability; tests of specific cognitive abilities are not analysed.

All cognitive tests followed an initial assessment of vision (Kay vision test; Kay, 1983) and hearing (Whisper hearing test; Prescott et al., 1999). The Kay vision test requires participants to match a series of images (presented one at a time in decreasing order of size at a distance of 3m) to the correct image out of eight possible options from a card in front of them. The Whisper test requires participants to point to the correct image out of eight possible images from a card in front of them when the name of an image is said at varying volumes from a distance of 50cm behind their ears.

Demographic information (e.g. years in education, accommodation type) and a detailed medical history (including whether the individual had a clinical diagnosis of dementia) was also obtained during this session. In addition to this, the Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities (CAMDEX-DS; discussed in section 1.3.3 Cognitive testing in DS) was obtained, which was used to determine whether an individual was showing any signs of cognitive decline. This was defined as decline on any one of the nine domains measured within the CAMDEX-DS (everyday skills, memory and orientation, general cognitive functioning, language, perception, praxis, executive functions, personality and behaviour, and self-care).

The Kaufmann's Brief Intelligence Test (KBIT-2) raw test score is the measure chosen from this battery for the purpose of this study. This was used to provide an estimate of general cognitive ability. Detailed discussion of the KBIT-2 (Kaufman & Kaufman, 2004) and its use as a tool in people with DS is discussed in section 1.3.3 Cognitive testing in DS. The KBIT-2 consists of three subtests that assess general cognitive abilities through questions relating to verbal knowledge, pattern completion and riddle completion. Raw scores were used due to a high number of participants at floor-level when scores are converted to age-adjusted IQ scores (i.e. an IQ of 40).

Participants were excluded from the study if they started but did not complete the KBIT-2, however where only the final KBIT-2 subtest (riddles) was missing due to non-completion, this data was generated based on the relationship between riddles and verbal knowledge subtests. This relationship was calculated using data from participants who completed both subtests. This technique is a form of multiple imputation, which is generally thought to provide the most accurate estimates of ability for continuous data (Finch, 2008). The equation for this relationship was: riddles score = $0.2 + (0.65 \times \text{verbal knowledge score})$. Participants who did not complete the KBIT-2 because they failed to understand the test instructions were given a score of zero.

3.5 Resting-state EEG paradigms

Two independent resting-state paradigms (EO and EC) were administered in a counterbalanced order between participants. The counterbalanced order was determined by participant number (previously assigned within the cognitive assessment), with even numbered participants completing the EO paradigm first and odd numbered participants completing the EC paradigm first. These resting-state

paradigms were carried out within a larger battery of EEG tests which also included an auditory-oddball ERP paradigm, an old-new object memory ERP paradigm, and a language-oddball ERP paradigm. This thesis is concerned only with resting-state activity; ERP paradigms are not analysed. Paradigms were programmed using E-Prime software.

The EO resting-state EEG paradigm consisted of continuous recording for 5.5 minutes while participants were seated 1m from an 28cm by 17.5cm LCD monitor displaying a muted cartoon clip (21cm x 16cm) of Disney's Fantasia, taken from the Nutcracker Suite section (viewing angle 16 degrees). A cartoon clip was chosen as opposed to a fixation-cross in order to improve participant compliance and also to improve alignment with infant resting-state protocols which included the viewing of a cartoon. The chosen clip showed a variety of dances with fairies, flowers, mushrooms and fish. The particular clip was chosen as it was visually interesting, did not have a strong plot or identifiable characters, and would be suitable for adults of a range of ages. Participants were instructed to remain quiet, sit still and watch the cartoon. During recording participants were continuously observed. Verbal prompts were used when necessary to maintain fixation and prevent movement and/or speech.

The EC resting-state paradigm consisted of continuous recording for 5.5 minutes. Participants were instructed to remain quiet, sit still and keep their eyes closed. Verbal prompts were used when necessary to prevent movement and/or speech or when it seemed apparent participants were falling asleep. Due to poor compliance with this protocol (e.g. forgetting to keep eyes closed, falling asleep) an amendment was made after 18 participants had been seen. The amendment consisted of splitting the recording into 11 blocks (30 seconds each) with a break in-between each. The break was used to remind participants of the instructions and also minimise the likelihood of sleep.

3.6 EEG data acquisition

Continuous EEG was recorded using appropriately sized EGI hydrocel high density sensor nets (containing 128 channel silver-silver chloride electrodes; see Figure 3.1). Electrodes were evenly distributed across the scalp, from nasion to inion and from left to right mastoids (although due to individual scalp differences electrode positions varied slightly between participants). Electrodes above and below each eye and beside the outer canthus of each eye recorded vertical (VEOG) and horizontal (HEOG) electro-oculogram respectively. Electrode impedances were maintained below 50 k Ω

during recording. At the start of each recording gain and zero calibration were performed. The EEG signal was referenced to the vertex during recording, and signals were recorded using a bandpass filter of 0.1-100 Hz, amplified using a gain of 10,000 and sampled at a rate of 250 Hz. Recordings were made using NetStation (Electrical Geodesics, Inc., Eugene, OR).

3.7 EEG processing

3.7.1 Pre-processing

All EEG pre-processing was performed offline using MATLAB software (version R2014b) installed with an EEGLAB toolbox (version 13.4.4) and an additional ERPLAB plug-in (version 4.0.3.1) (Delorme & Makeig, 2004; Lopez- Calderon & Luck, 2014). The continuous EEG signal was digitally filtered using a lowpass filter of 30Hz. All data obtained from six ear electrodes were removed due to issues relating to morphological variation of ear location in the DS population. Namely, electrodes intended to surround the ear (numbers 44, 48, 49, and 113, 114, 119) were often on the ear itself and so these electrodes were discounted from all participants. Segments containing movement and/or eye movements (e.g. blink artifacts) were removed manually through visual inspection of the data from all remaining channels. The use of Independent Component Analysis (ICA) to remove blink artifacts was not utilised as data obtained during blinks in EO recording and data obtained during instances of eye-opening in EC recordings was unwanted.

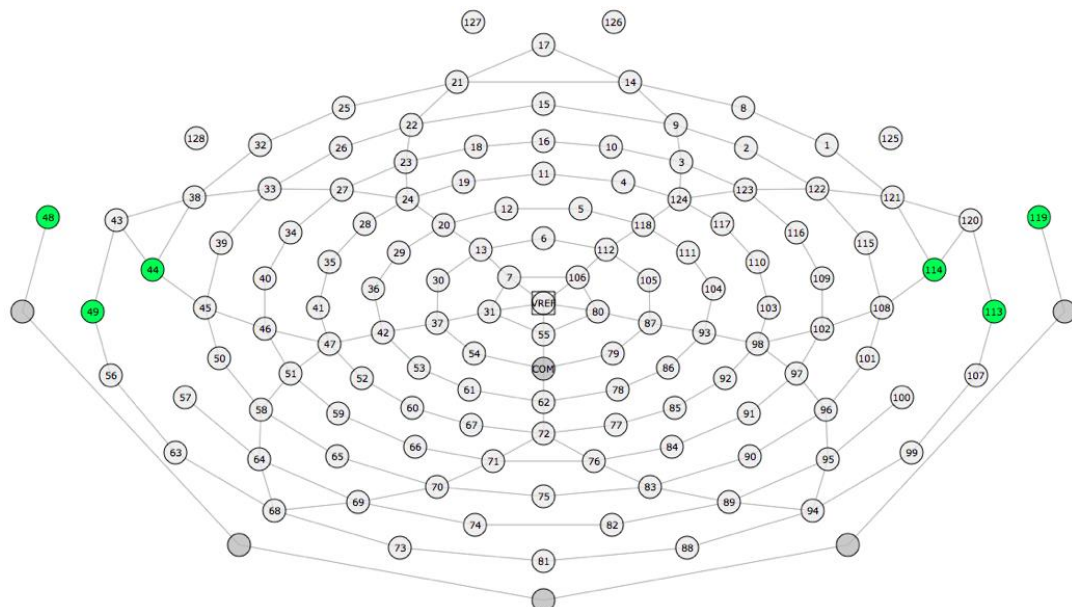


Figure 3.1 EEG electrode map

Electrode map illustrating individual cap electrodes intended to surround the ear that were excluded for all participants (numbers 44, 48, 49, and 113, 114, 119).

Bad channels were replaced using spherical spline interpolation and remaining channels were re-referenced to the average electrode (with the exception of the eye electrode channels which were removed from analysis following the manual removal of blink artifacts; numbers 125, 126, 127 and 128). Datasets were then segmented into 2-sec epochs. Recordings with less than 12 segments remaining were excluded from further analysis.

3.7.2 EEG measures

Early EEG analysis methods relied on the visual inspection of oscillatory activity recorded with an oscillograph. With the advent of digital technology and increased computing power there are now a wide range of methods available which can decompose an EEG signal into its spectral and temporal components for the purpose of more complex analysis.

It was outlined in section 2.2 that resting-state paradigms typically discard temporal information and focus instead on spectral information — that being the frequencies that are present in the signal, in which signals are represented as a linear combination of oscillatory functions (Gross, 2014). Various spectral analysis methods can be used to decompose the EEG signal in this way, with such methods involving Fourier analysis. Traditional Fourier analysis decomposes EEG signals into fixed-length sinusoidal functions, with varying amplitude and phase across frequency (van Vugt et al., 2007). Due to limitations of traditional Fourier analysis, such as relatively poor time–frequency resolution (Bruns, 2004), alternative methods such as wavelet and multitaper analysis have been developed to overcome these limitations by using a number of different window lengths which are then averaged. Power estimates obtained using these methods are thought to be more reliable than traditional Fourier methods (Thomson, 1982; Percival & Walden, 1993; van Vugt et al., 2007). EEG measures in this thesis were obtained using wavelet methods (Chapter 5 and 6), however for the purpose of DCM analysis, multitaper methods were used in Chapter 7.

Furthermore, both absolute and relative power values were calculated and analysed within chapter 5. Relative power provides a “normalised” measure of activity in each frequency band. It can be achieved on an individual basis by dividing absolute (raw) values for each individual by their total activity across the EEG spectrum. This method

helps to account for differences in broadband power across participants and therefore may be considered particularly important in individuals with DS, due to a higher degree of anatomical variation (Lee et al., 2016), for example.

Importantly, some participants included in this thesis did not have a measurable alpha peak within the selected frequency range (instead having a downward slope with peak frequency assigned to the lower boundary of this using standard methods; i.e. 8 Hz using a standard alpha band). Alpha peak features were therefore obtained for all individuals by removing the individual linear trend from the EEG spectrum to achieve “spectral normalisation” (Demanuele et al., 2007). This method allowed an accurate representation of these values to be obtained for all individuals, including those whose peak characteristics were lost within the natural EEG background noise (1/f noise; brain signals show a decrease in power with increasing frequency). Due to slowing of the EEG spectrum for some individuals, an extended alpha band (theta-alpha; 4-13 Hz) was employed for peak analyses within Chapter 6.

3.8 Data analysis

The following chapters contain analyses relating to the feasibility and generalisability of obtained recordings (Chapter 4), differences in EC spectral measures between individuals with DS and age-matched TD control subjects (Chapter 5), the relationship between EO and EC EEG spectral measures and age and general cognitive ability within adults with DS (Chapter 6), and the modelling of cortical circuitry underlying EEG oscillations of interest (Chapter 7). Full methodological descriptions for these analyses can be found within the relevant chapters.

Chapter 4 Analysis of participant sample and paradigm feasibility

4.1 Introduction

This EEG study is uniquely nested within a larger project involving 315 adults with DS (LonDownS; see Chapter 3 General Methods). Participants taking part in the EEG are a subpopulation (n=88) of this larger sample. To date there has been no published analysis of the extent of bias within samples with DS taking part in neuroimaging research, or research related to the extent of bias in paradigm completion within such studies. This is an important issue to explore in order to assess the potential generalisability of research findings to a larger population of adults with DS.

In addition to exploring bias, a further issue that warrants investigation is the overall feasibility of obtaining baseline EEG recordings in individuals with DS. In particular, inability to achieve sustained voluntary eye-closure and issues of sleep occurring during recordings may influence paradigm completion. Previous studies identified within the literature review of this thesis (section 2.4) fail to report such issues (although there is a suggestion of issues with eye-closure occurring in literature by Babiloni et al. (2009; 2010), who noted participants unable to close their eyes had their eyelids held down). Investigating the feasibility of obtaining different baseline recording paradigms in individuals with DS is therefore an important issue for informing study design within this population.

There are a number of broad stages involved in the acquisition of EEG data from individual participants (see Figure 4.1). Within this study, each individual must have first taken part in the wider LonDownS study in order to have been eligible to be invited to participate in the EEG (in addition to meeting specific inclusion criteria outlined in the methods section below). Having been invited to participate in the EEG, the next stage was whether individuals participated or did not participate in the recording session. Factors influencing this may have included the participant's own wishes but also those relating to practical issues, including whether family members and/or carers were able to accompany the individual to the session. Finally, once individuals have consented to participate in the study, EEG resting-state data collected during the recording session ranged between a single paradigm completed (EO or EC) to both paradigms completed. There were also two different EC protocols used in this study (discussed in

Chapter 3 General Methods), of which each participant was given the opportunity to complete only one.

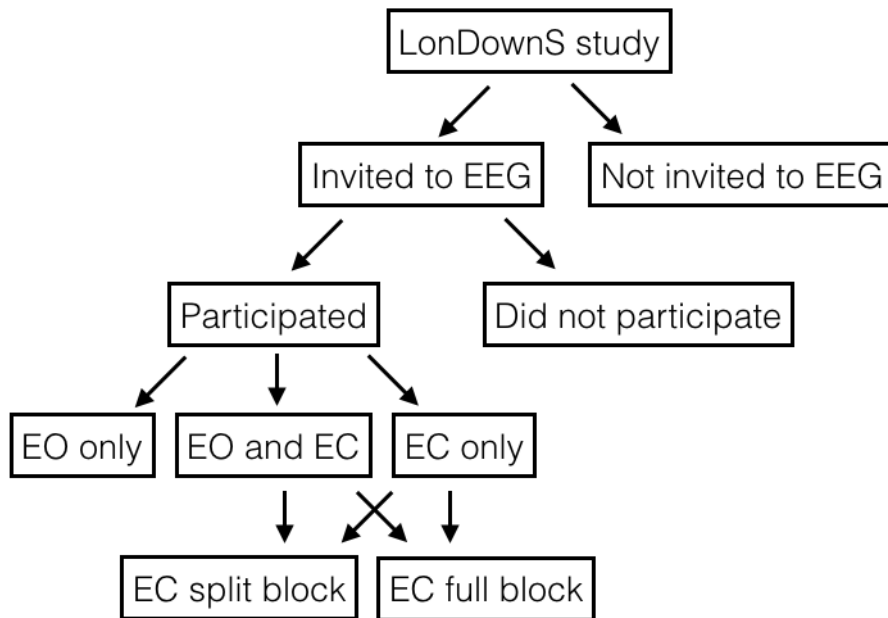


Figure 4.1 EEG participant flow diagram

Flow chart illustrating the EEG participant pathway. Outcomes of participants participating in the EEG include EO data only, EC data only, or both EO and EC data. All EC data was obtained from either a full block or split block recording paradigm. An additional outcome (not shown here) is that of no data, occurring due to technological issues (discussed in 4.3.5 Overall paradigm feasibility section) or participant exclusion. See Figure 4.2 for numbers at each stage.

4.1.2 Aims

The primary aim of this chapter was to explore the nature and extent of potential bias within the sample of individuals with DS participating in this study. In order to determine the source of any bias it is necessary to explore differences between participants who have been invited and not invited to take part in the EEG session, in addition to differences between invited participants who have participated and not participated. Factors that will be explored include participant age, general cognitive ability, presence of dementia, and accommodation type. Accommodation type is included as a factor because it is thought this may influence who accompanies the participant to the session (e.g. paid carer or family member). This in turn may influence participation, as

services may not be able to provide the several hours of one-to-one care necessary to accompany the participant.

A secondary aim of this chapter was to explore potential factors influencing data collection from differing resting-state paradigms in participants with DS (including EO and variations of EC paradigms).

The overall aim of this chapter was to describe the population of individuals with DS participating in this EEG study relative to a larger sample of individuals with DS. As such, no formal hypotheses were tested.

4.2 Methods

4.2.1 Participants

Participants were recruited from the LonDownS participant pool of adults (detailed in Chapter 3 General Methods). As detailed in the General Methods section, all individuals from the LonDownS participant pool who met the following criteria were invited to take part:

- i) lived within a reasonable day's return travelling distance to the EEG laboratory in central London
- ii) individual would be able to tolerate wearing an EEG cap for up to an hour (based on interactions and discussions with participants, parents and/or carers during the initial cognitive assessment, and through later telephone and email correspondence)
- iii) participants had adequate hearing and vision (assessed during the initial cognitive session using Kay vision test (Kay, 1983) and Whisper hearing test (Prescott et al., 1999) respectively)
- iv) Participant did not have an acute physical or mental health condition

As discussed in the General Methods chapter of this thesis, the Kay vision test requires participants to match a series of images presented in decreasing order of size. A threshold of 3/19 was used to identify participants with significant visual difficulties. Participants not meeting this threshold were excluded from the LonDownS cognitive

sample. For the Whisper test, participants unable to respond correctly to at least a loud voice were excluded from the LonDownS cognitive sample. Participants excluded at this stage are not included within the analysis of this chapter (i.e. they are not counted as “not invited” but are excluded entirely).

4.2.2 Cognitive, clinical and demographic variables

All cognitive, clinical and demographic variables investigated were collected at the initial cognitive assessment session (however it was checked at the EEG session whether dementia status had changed in the time between sessions). Details of length of time between sessions are outlined in Chapter 3 General Methods.

Raw KBIT-2 score was used to provide a measure of estimated general cognitive ability (discussed within Introduction and General Methods chapters). Accommodation type was assigned as one of two groups: living in care/with a paid carer or living with family/independently. These categories were chosen in order to reflect whether participants were most likely to be accompanied to the session by either a paid carer or a family member. Dementia status (dementia or no dementia) was defined based on clinical diagnosis (ascertained by questioning of family and/or carers about whether the participant had received a clinical diagnosis of dementia). Age of each participant at their cognitive assessment was used for study participation analysis (invited/not invited and participated/did not participate), whereas age at EEG was used for paradigm analysis.

Results of genetic testing (obtained through the collection of saliva or blood samples at the initial cognitive assessment) were not available at the time of EEG recruitment and data collection. Participants with a form of DS other than Trisomy 21 (e.g. mosaic or translocation) have therefore not been excluded in this chapter.

4.2.3 EEG recording paradigms

All participants taking part in the EEG session had the opportunity to complete both an EO and EC resting-state paradigm (each of 5.5 min recording duration). In the EO paradigm participants were instructed to sit still and watch a cartoon (described in the General Methods chapter). In the EC paradigm participants were instructed to sit still with their eyes closed.

As discussed in the General Methods chapter, after 18 participants had completed the EEG session, the EC paradigm was amended to a 'split' structure to incorporate a scheduled break every 30-seconds. Recording only continued after each 30-second recording block if the participant was happy to do so and if the researcher was satisfied they were fully awake and were able to adhere to the instruction of keeping their eyes closed.

Full details on data acquisition and pre-processing are provided in the General Methods chapter. For the purpose of this chapter, data quality was defined as the number of 2-second artifact free epochs obtained from each recording.

4.2.4 Statistical analysis

Differences in dementia status and accommodation type between groups were explored using chi squared tests. Differences in age and raw KBIT-2 score between groups were explored using independent samples t-tests (a histogram was used to verify normal distribution and Levene's test was used to verify homogeneity of variances). Independent samples t-tests were also used to investigate if there was a difference in age or KBIT-2 scores for individuals completing the full-block or split-block EC paradigms, and to investigate data quality (number of 2-second artifact free epochs) between EC recording paradigms. A paired samples t-test was used to investigate data quality between EO and EC conditions. One-way ANOVAs were used to explore differences in age and KBIT-2 score between participants completing the EO only, EC only or both recording paradigms.

4.3 Results

4.3.1 Participant sample

A total of 31 participants were excluded from the LonDownS cognitive sample (n=315) due to either failing screening tests for hearing or vision (n=21) or non-completion of the KBIT-2 test (n=10), leaving a sample of 284 participants for analysis. Twenty-eight of these 284 participants had not completed the riddles KBIT-2 subscale and so this was imputed (two of these 28 participants took part in the EEG session). KBIT-2 imputation methods are described in section 3.4.

Table 4.1 describes the demographics, KBIT-2 raw scores and diagnostic dementia status of the LonDownS participant pool (n=284), the subgroup of individuals invited to attend the EEG session (n=164), and the subgroup of these individuals taking part in the EEG session (n=88). Six participants attended the EEG session but chose not to take part on arrival, and so were categorised as not participating. See Figure 4.2 for a flow chart of participant numbers at each stage of the EEG pathway. Variables of age and KBIT-2 were considered normally distributed in all samples according to histogram shape (including the two samples not shown in Table 4.1 of participants not invited and invited participants not taking part).

	Total	Age in years (SD)	Gender	Raw KBIT-2 (SD)	Dementia diagnosis
LonDownS sample	284	39.14 (13.76)	144 (50.70%) M; 140 (49.30%) F	39.75 (25.74)	47 (16.55%)
Sample invited to EEG	164	38.19 (13.46)	83 (50.61%) M; 81 (49.39%) F	44.34 (23.82)	18 (10.98%)
Sample participating	88 (53.33%)*	34.01 (12.09)	46 (52.27 %) M; 42 (47.73%) F	46.89 (22.76)	7 (7.95%)

Table 4.1 Participant demographic information

Mean (SD) of demographic information, raw KBIT-2 score and diagnostic dementia status (percentage of sample shown) of all participants taking part in the LonDownS sample, the subgroup of individuals invited to EEG, and the subgroup of those individuals taking part in the EEG session. *refers to percentage of individuals who participated in the session out of the sample invited

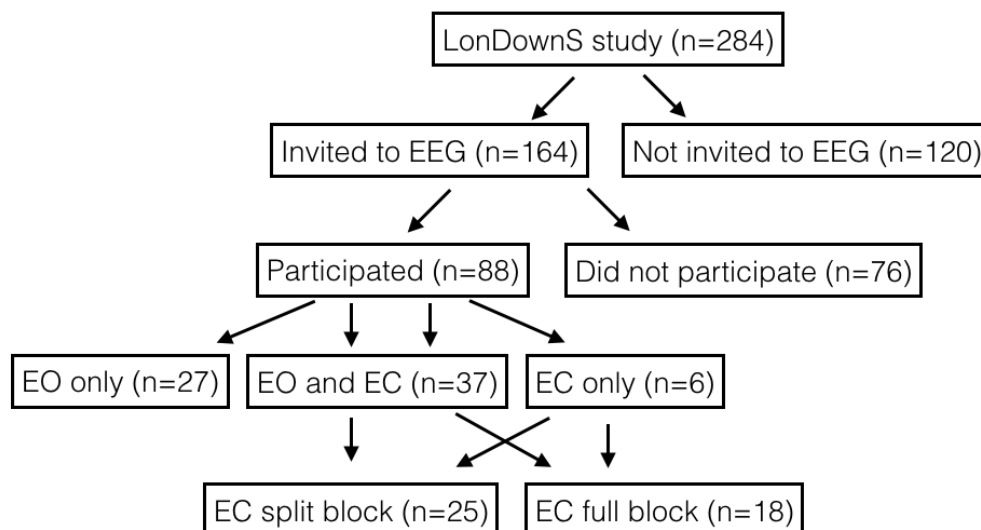


Figure 4.2 Number of participants at each pathway stage

Flow chart showing the number of participants at each level (n) of the EEG pathway in this study. Outcomes of participants participating in the EEG include EO data only, EC data only, or both EO and EC data. Outcome of no data (n=18) is not shown; details provided in section 4.3.5.

4.3.2 Dementia prevalence in the EEG sample

To investigate the prevalence of dementia in the EEG sample, chi squared tests were used to compare the number of participants with a clinical diagnosis of dementia between individuals invited to take part in the EEG study (n=164) and those not invited (n=120), and between invited individuals taking part (n=88) and those not taking part (n=76).

There was a statistically significant difference in dementia diagnosis between those who were invited (n=18 individuals with dementia out of 164 participants; 10.98%) and those who were not invited (n=29 individuals with dementia out of 120 participants; 24.17%), $\chi^2 (1) = 8.73$, $p = .003$. There was no statistically significant difference in dementia diagnosis between those who took part (n=7 individuals with dementia out of 88 participants; 7.95%) compared to those who did not take part (n=11 individuals with dementia out of 76 participants; 14.47%), $\chi^2 (1) = 1.77$, $p = .183$. This indicates there were significantly fewer individuals with a diagnosis of dementia invited to the EEG assessment, however of those invited, there was no significant difference in participation between individuals with and without dementia.

4.3.3 Age and ability in the sample

Independent samples t-tests were used to investigate age and KBIT-2 score of individuals invited to take part in the EEG study compared to those not invited, and to investigate age and KBIT-2 score of invited individuals who took part compared to those who did not take part. Results are summarised in table 4.2.

	Age (years)	KBIT-2
Invited / not invited	t (282) = 1.37, p = .172 (equal variances assumed), 95% CI [-.99, 5.51]	t (282) = -3.58, p < .001 (equal variances assumed), 95% CI [-16.82, -4.90]
Mean age (SD)	Not invited M = 40.45 (14.10); invited M = 38.19 (13.46)	Not invited M = 33.48 (27.02); invited M = 44.34

		(23.82)
Took part / did not take part	t (162) = 4.53, p < .001 (equal variances assumed), 95% CI [5.01, 12.95]	t (162) = -1.48, p = .141 (equal variances assumed), 95% CI [-12.83, 1.85]
Mean age (SD)	Took part M = 34.01 (12.09); Did not take part M = 43.03 (13.42)	Took part M = 46.89 (22.78); Did not take part M = 41.39 (24.80)

Table 4.2 Age and KBIT-2 score group comparison

Mean (SD) and results of independent samples t-tests for age and KBIT-2 score of all individuals invited to take part in the EEG study compared to those not invited, and all individuals who took part compared to those who did not take part.

These results show that although there was no significant difference in age between individuals invited and not invited to take part in the EEG, invited individuals had significantly higher general cognitive ability (M = 44.34 (23.82 SD)) than those not invited (M = 33.48 (27.02 SD)). Of those invited, individuals taking part did not significantly differ in terms of general cognitive ability but were significantly younger (M = 34.01 (12.09 SD)) compared to those not taking part (M = 43.02 (12.42 SD)).

4.3.4 Effect of accommodation type in the sample

In order to explore whether accommodation type was significantly associated with invitation to EEG or participation in the EEG this was explored in both groups using Pearson chi squared tests. Accommodation type was categorised as either living in care/with a paid carer or living with family/alone.

There was no significant difference in accommodation type between individuals invited (n=87 in care/with a paid carer (53.05%); n=77 with family/alone (46.95%)) and not invited (n=73 in care/with a paid carer (60.83%); n=47 with family/alone (39.17%)) to the EEG, $\chi^2 (1) = 1.71, p = .191$. There was also no significant difference in accommodation type between invited individuals taking part (n=43 in care/with a paid carer (48.86%); n=45 with family/alone (51.14%)) and not taking part (n=44 in care/with a paid carer (57.89%); n=32 with family/alone (42.11%)) in the EEG, $\chi^2 (1) = 1.34, p = .248$. This suggests accommodation type was not significantly associated with either invitation to take part in the EEG or participation of those invited.

4.3.5 Overall paradigm feasibility

Eighteen of the 88 individuals who took part in the EEG session were not included for this stage of analysis due no useable resting-state data obtained. For 16 of the 18 individuals this was due to technological issues (>10% bad electrodes, computer/software crash during recording, and corruption of saved files). The remaining two individuals out of these 18 completed only the EO paradigm, but were excluded from this due to falling asleep (n=1) or due to <12 segments of artifact-free data (n=1; 10 segments obtained) within this recording.

No further datasets were excluded due to sleep or insufficient number of segments. It should be noted, however, all other instances of participants falling asleep during a recording were categorised as non-completion, as in these instances the recording was stopped before it had finished (unless the participant had fallen asleep within a recording block of the EC paradigm, in which case that block was discarded and the remaining data utilised).

In total, usable EEG data from at least one paradigm was obtained from 70 participants (see Table 4.3). Where participants completed only one paradigm (EO or EC), this was due to either not consenting to the other paradigm, consenting but being unable to follow the task instructions (i.e. watch the cartoon/close your eyes), asking to stop the paradigm before the recording had finished, or the recording being terminated due to falling asleep (outlined above).

	Total	Age in years (SD)	Gender	Raw KBIT-2 (SD)	Dementia (n)
EO only	27	34.41 (12.30)	13 M (48.15%); 14 F	39.74 (22.36)	2 (7.41%)
EC only	6	40.17 (15.12)	4 M (66.67%); 2 F	39.17 (28.21)	2 (33.33%)
Both EO and EC	37	30.86 (10.90)	18 M (48.65%); 19 F	54.84 (19.80)	1 (2.70%)

Table 4.3 Demographic information relating to obtained data

Mean (SD) of demographic information, raw KBIT-2 score and dementia diagnosis (number of individuals) of all participants taking part in the EEG session for whom useable data was obtained for at least one recording paradigm (n=70).

One-way ANOVAs were used to investigate how the three completion groups (EO only, EC only, both EO and EC) differed in terms of age and KBIT-2 score. According to histogram shape variables of age and KBIT-2 were considered normally distributed and

Levene's statistics were not significant indicating the assumption of homogeneity of variances was met for both variables.

There were no statistically significant differences between group means for age determined by one-way ANOVA, ($F(2,67) = 2.23, p = .116$). There was a statistically significant relationship between group means for KBIT-2 ($F(2,67) = 4.35, p = .017$). A Tukey post hoc test revealed a significantly higher KBIT-2 score ($p=.020$) in the 'both' completion group ($M = 54.84, SD = 19.80$) compared to the 'EO only' group ($M = 39.74, SD = 22.36$). The difference in KBIT-2 score between the 'both' completion group and the 'EC only' completion group ($M = 39.17, SD = 28.21$) was not statistically significant ($p=.231$), neither was the difference between the 'EO only' and 'EC only' completion groups ($p = .998$). These results suggest that although age is not significantly associated with paradigm completion, individuals able to complete both EO and EC recording paradigms had significantly higher general cognitive ability than those only able to complete the EO recording paradigm.

In order to investigate paradigm feasibility, the number of 2-second artifact-free epochs obtained from EO and EC paradigms (normal distribution according to histogram shape for both) were compared using a paired sample t-test to determine whether data quality significantly differed between conditions. Participants in this sub-population only included those for whom both EO and EC data was obtained ($n = 37$) in order to ensure comparisons between conditions were valid (see Table 4.4). There was no statistically significant difference in the number of 2-second epochs obtained from the EC ($M = 45.70, SD = 24.57$) compared to the EO ($M = 36.51, SD = 25.55$) condition, $t(36) = 1.80, p = .080, CI [-1.17, 19.55]$. This indicates no significant difference in data quality between recording conditions.

	Mean (SD) 2-sec segments
EO paradigm	36.51 (25.55)
EC paradigm	45.70 (24.57)

Table 4.4 Segments obtained

Mean (SD) of number of 2-second artifact-free segments obtained from each recording paradigm, including only participants where both paradigms were completed ($n=37$).

4.3.6 Assessment of EC paradigm feasibility: full block vs. split block

	Total	Age in years (SD)	Gender	Raw KBIT-2 (SD)	Dementia (n)
Full-block EC paradigm	18	31.56 (9.84)	8 M (44.44%); 10 F	51.72 (21.60)	1 (5.56%)
Split-block EC paradigm	25	32.60 (13.25)	14 M (56.00%); 11 F	53.32 (21.79)	2 (8.00%)

Table 4.5 Demographic information for each EC paradigm

Mean (SD) of demographic information, raw KBIT-2 score and dementia diagnosis (number of individuals) of all participants completing an EC recording paradigm for whom useable data was obtained ($n=43$), according to EC paradigm undertaken (either full-block or split-block protocol).

In total usable EC EEG data was obtained from 43 participants (see Table 4.5). Independent samples t-tests were used to investigate age and KBIT-2 score of individuals completing the full-block EC paradigm compared to those completing the split-block EC paradigm.

According to histogram shape, variables of age and KBIT-2 were considered normally distributed in this participant sub-sample. Levene's statistic was not significant for KBIT-2 however this was significant for age ($F = 4.43$, $p = .041$) and so equal variances were not assumed for this variable. There were no statistically significant differences of KBIT-2 (full-block $M = 51.72$ (21.60 SD); split block $M = 53.32$ (21.79 SD); $t = -.24$ (41), $p = .813$) or age (full-block $M = 31.56$ (9.84 SD); split block $M = 32.60$ (13.24 SD); $t = -.30$ (40.94), $p = .768$) between either EC paradigm completion group. This suggests there were no significant differences in age or general cognitive ability between participants completing each EC recording paradigm.

An independent samples t-test indicated there was no statistically significant difference in data quality (number of epochs obtained; normal distribution according to histogram shape and equal variances assumed) between the full block ($n = 18$; $M = 44.17$ (26.66 SD)) and split block ($n = 25$; $M = 44.04$ (21.04 SD)) EC recording paradigms (t (41) = .02, $p = .986$, CI [-14.56, 14.82]). This indicates there is no significant difference in the amount of useable data obtained from the two EC resting-state paradigms.

4.4 Discussion

4.4.1 Summary of findings

In the present study, there were significantly fewer individuals with a diagnosis of dementia invited to the EEG assessment than those not invited. Invited individuals also had significantly higher general cognitive ability than those not invited. There was no significant difference in age or accommodation type between invited individuals and those not invited.

Participating individuals were significantly younger compared to those who were invited but did not participate. There was no significant difference in cognitive ability or dementia prevalence between invited individuals participating and not participating. There was also no significant difference in accommodation type between invited individuals participating and not participating.

In terms of paradigm completion, this was not significantly associated with age, however individuals able to complete both EO and EC recording paradigms had significantly higher general cognitive abilities than those only able to complete the EO paradigm. Interestingly there was no significant difference in the number of 2-second artifact free segments obtained between the two conditions and between the two EC recording paradigms.

4.4.2 Research in context, strengths, limitations and future research

To date there has been no published analysis exploring the representativeness of participants with DS attending neuroimaging studies. The current study helps to describe the ways in which these samples and data from resting-state paradigms may be biased, informing study design and generalisability of findings.

These findings suggest that within this EEG study a bias was introduced into the sample at the stage of participant invitation, with individuals of higher ability invited and fewer people with dementia being asked to participate. For pragmatic reasons a degree of selection bias is inevitable due to the requirement to tolerate wearing the EEG cap. Future studies could take steps to minimise this, however. For example providing resources for participants, parents and/or carers would allow individuals to make an informed assessment of ability to tolerate the EEG cap. Such resources could include video examples of the EEG cap being worn by other participants. A basic checklist including relevant questions (e.g. "Would the participant be comfortable

having their head touched?) may also be useful for the purposes of assessing and recording formally how participants meet the criteria of being able to tolerate the cap. Further possibilities include enabling participants to try the EEG cap prior to the recording session, for example in the case of this study taking a cap to the initial cognitive assessment may have been useful. Such steps may help reduce potential bias, however it remains that the ability to tolerate equipment is necessary for all neuroimaging studies into ID populations and dementia populations, and consequently all samples are likely to contain similar biases. Advances in technology improving the comfort of equipment may reduce this in the future.

The finding that participating individuals were significantly younger than invited individuals who did not participate could be due to it being potentially harder for older individuals to travel into central London (for instance due to increased likelihood of health and mobility problems). Accommodation type or presence of dementia are not likely to be factors as these were explored in the current study and were found to be not significantly different between those taking part and not taking part. It may still be the case, however, that the person accompanying the participant (i.e. family member or paid carer) is a factor but accommodation type may be a poor measure of this. The assumption that individuals living in care/with a paid carer would be accompanied by a paid carer for the EEG session is a limitation of this study. Future studies exploring the source of potential bias in ID samples could benefit from enquiring who would potentially be accompanying the participant at the stage of invitation, and recording this information on attendance.

It is possible that portable EEG equipment may assist future studies in reducing the potential impact of poor health or mobility and accommodation factors on the participant sample. Using portable equipment would also increase overall sample size as the exclusion criteria of being within a day's return travelling distance to London would no longer be necessary.

A strength of this study is that it attempted to be as inclusive as possible, with individuals of all ages and ability who met the basic inclusion criteria (including those with a diagnosis of dementia) invited to take part. As a consequence of this there was a large proportion of individuals unable to complete both resting-state paradigms during the session. It was found that more participants completed the EO paradigm compared to the EC and participants able to complete both recording paradigms had greater general cognitive ability than those only able to complete the EO recording paradigm. These findings are likely due to the EC task being more difficult (and potentially less

enjoyable and familiar), requiring participants to understand and execute the instruction of closing their eyes and maintain this instruction in working memory. In contrast to this, the EO recording paradigm of watching a video is a passive activity that participants are familiar with. It is possible that completion of EC paradigms could be improved by asking participants to practice closing their eyes for short durations of time before attending the session. Participants would then be more familiar with the task and have had the opportunity to practice this if necessary.

The absence of a significant difference in number of 2-second artifact free segments obtained from the different conditions among individuals able to complete both recordings and different EC paradigms suggests a similar level of movement artifacts between these. Eye-closure does therefore not appear to improve data quality in terms of movement artifacts, nor does incorporating regular breaks into the EC paradigm improve data quality within this. However, this analysis only included participants able to complete both recording paradigms. Findings may therefore be less applicable to individuals of lower cognitive ability.

An additional aim of splitting the EC recording block was to reduce the likelihood of participants entering light sleep during recording without the researcher being aware of this occurring. It is likely this was achieved, however this would not be apparent from the data quality measure used here. Using the EEG spectrum to investigate entry into stage 1 sleep may be possible, however this could be problematic in individuals with DS as it has been suggested that the awake power spectrum can be similar to that of early sleep stages (e.g. Clausen et al., 1977).

A further limitation of this study is that comparing a sub-population of participants to the larger research sample from which they were recruited is problematic, as the larger sample is likely to be biased towards individuals who are more likely to engage with research. Attempts were made, however, for the larger LonDownS sample to be as representative as possible by utilising a variety of recruitment pathways across England and Wales, including a network of NHS trust sites to identify and approach potential participants. Despite this it is possible that the true skew of the EEG sample when compared to the wider DS population may be greater than that detailed in this study.

4.4.4 Conclusions

The findings of this chapter suggest that the EEG sample within this thesis is biased in terms of a younger age and greater general cognitive ability compared to a larger DS sample. The issue of skew towards individuals with greater cognitive ability is exacerbated further when considering individuals able to complete both recording paradigms. It is likely such bias is a common limitation of all EEG studies in DS and is not unique to this particular study. Future studies may benefit from improving the way it is determined whether participants would be able to tolerate wearing EEG equipment in order to reduce this potential source of skew. Studies may also benefit from using portable equipment and asking participants to practice closing their eyes for short intervals before attending the session. Although splitting the EC recording did not reduce movement artifacts in the data this may still be beneficial in terms of reducing sleep incidence, however further research is needed to investigate this.

Chapter 5 Eyes-closed resting-state EEG: comparison between adults with Down syndrome and typically-developing controls

5.1 Introduction

The focus of this thesis is on individual differences in adults with DS, however understanding primary differences in resting-state activity between those with DS and TD control subjects will help elucidate the importance of findings within subsequent chapters and inform the overall conclusions of the thesis. For this reason, a group of chronologically age- and sex- matched TD control subjects was selected from an open source dataset of eyes-closed resting-state EEG activity for comparison with the data collected from participants with DS. This chapter details this analysis and findings.

The use of open source datasets is becoming increasingly common in neuroimaging research. Although not without their limitations — including inherent differences between datasets in terms of equipment, experimental protocols and experimenter effects — open source datasets offer numerous benefits including increased efficiency, transparency, and reproducibility of research (Gilmore et al., 2017). One such EEG-based dataset is provided by the Child Mind Institute (an American non-profit organisation focusing on childhood mental health and learning disability, and dedicated to the support of open science projects (see childmind.org)). The resource, named the Multimodal Resource for Studying Information Processing in the Developing Brain (MIPDB), aims to advance the study of clinical cognitive neuroscience (Langer et al., 2017). It contains high-density task-based and task-free raw EEG data (including eyes-closed resting-state) collected from 126 TD individuals aged 6-44 years.

Differences in resting-state EEG power and frequency measures between individuals with DS and TD controls reported by previous studies are detailed within the literature review in Chapter 2. Alpha activity (typically defined as 8-13 Hz) has been of interest to researchers from the earliest studies. Differences in alpha activity are commonly reported, though results are contradictory. For alpha frequency, a number of studies have reported a significantly slower peak frequency in DS (Ono et al., 1992; Soininen et al., 1993; Murata et al., 1994; Locatelli et al., 1996; Velikova et al., 2011). Some studies, however, report no significant differences in alpha frequency (Politof et al., 1996; Babiloni et al., 2010). Results pertaining to alpha power differences are also

conflicting, with some studies reporting increases (Partanen et al. 1996), others reporting decreases (Babiloni et al., 2009; Medaglini et al.1996; Locatelli et al., 1996), and some finding no difference (Politoff et al., 1996) in individuals with DS compared to TD controls.

In contrast, power in slow (delta and theta) and fast (beta and gamma) EEG bands has been reported as greater in participants with DS compared to TD controls on a fairly consistent basis (Ono, 1993; Murata et al., 1994; Medaglini et al.1997; Partanen, et al., 1996; Politoff et al., 1996; Locatelli et al.,1996; Babiloni et al., 2009; Babiloni et al., 2010; Velikova et al., 2011), although Babiloni et al. (2009, 2010) reported reduced power in fast frequencies in individuals with DS compared to controls, and Politoff et al. (1996) reported no significant difference in absolute gamma power. Results regarding faster frequencies may therefore be slightly inconsistent. Sources of inconsistencies between studies may be due to methodological differences, including differences in frequency band classification and locations examined, or differences in participants' age between studies.

When considering differences in findings based on absolute and relative power values, a small number of studies have examined both. Locatelli et al. (1996) and Medaglini et al. (1996) reported the same findings for absolute and relative values, with absolute and relative power in delta, theta and beta bands being significantly higher and absolute and relative alpha power being significantly reduced in DS compared to controls. It should be noted, however, these two studies are likely to be of the same sample (discussed in section 2.4.1.4). In contrast to these findings, Politoff et al. (1996) reported there were no significant differences between individuals with DS and controls using relative power values, despite finding significantly higher absolute power for delta, theta and beta bands in those with DS. It is therefore possible that absolute and relative values may yield either the same or different results when comparing EEG variables between individuals with DS and controls.

As previously discussed within the literature review in Chapter 2, differences in resting-state EEG power and frequency measures between individuals with DS and TD controls may differ topologically. In summary, although results are inconsistent, there is an indication that differences in alpha activity between these two groups may be most apparent in posterior regions (Medaglini et al.1997; Locatelli et al.,1996) and may also differ between occipital and parietal electrode derivations (Ono et al., 1993). In contrast, the higher power in delta activity in individuals with DS compared to TD controls may most be apparent in frontal and centro-anterior regions (Babiloni et al

2009; Medaglini et al.1997; Locatelli et al.,1996), and the higher theta power in those with DS most apparent in centro-posterior regions (Medaglini et al.1997; Locatelli et al.,1996). For beta activity, the higher power in individuals with DS may be most apparent in parieto-temporal regions (Medaglini et al.1997; Locatelli et al.,1996). Consequently it appears important to analyse spectral differences between individuals with DS and TD controls across the scalp as topographical differences may exist.

5.1.2 Aims and hypotheses

This chapter aimed to use common analysis methods to determine differences in EEG activity (band power, peak amplitude and peak frequency) between adults with DS and TD age- and sex- matched control subjects. Based on previous findings, it was hypothesised that individuals with DS would have less power in the alpha band (8-13 Hz) and more power in other EEG bands (delta (0.5-4 Hz) theta (4-8 Hz) and beta (13-30 Hz)). Gamma band activity was not examined in this study due to the high likelihood of muscle artifacts (which share a similar frequency to the gamma band) within this region of the EEG spectrum.

The use of common analysis methods reduces methodological variation, through the use of classical frequency bands and a standard occipital electrode montage. Due to the indication of topographical EEG differences in DS compared to TD controls, however, a second frontal electrode site was chosen for additional analysis. Furthermore, both absolute and relative power values were calculated and analysed (detailed in Chapter 3: General Methods).

Secondary aims were to determine whether between-group comparisons differed for power results obtained from absolute and relative values, and whether between-group comparisons differed for results obtained from occipital and frontal derivations. It was hypothesised that absolute and relative values would not yield different between-group comparison results. It was also hypothesised that between-group comparison results from occipital and frontal derivations would not differ.

5.2 Methods

5.2.1 Participants

TD control participants aged 16 or over from the MIPDB (from a possible 39 individuals) were age- and sex- matched to participants with DS for whom sufficient EC resting-state data (≥ 12 2-second segments) had been obtained. Only participants with DS who did not show evidence of cognitive decline or have a diagnosis of dementia, and who had genetically confirmed trisomy 21, were included for this analysis (a possible 36 individuals). In total 26 individuals were age-matched to within 1 year. Sex-matching was achieved on a subgroup-level (16-25 years, 26-35 years, 36 years and over) and was identical for groups 16-25 years and 26-35 years. However, due to the small number of control participants aged 36 and over ($n=4$), for this group sex-matching was 3M:1F for controls to 1M:3F for those with DS. One control participant was excluded due to their EEG data classed as an outlier. As there was no suitable alternative control participant for matching, their matched participant with DS was also removed from analyses.

The following is an list of inclusion criteria for individuals with DS in this chapter:

- Sufficient EC resting-state data (≥ 12 2-second segments) was obtained from the participant during the EEG testing session
- Participant has genetically confirmed trisomy 21
- Participant did not show evidence of cognitive decline or have a diagnosis of dementia at the time of cognitive assessment

5.2.2 EEG acquisition

Data from both groups was acquired using 128-channel EEG Geodesic Hydrocel nets (EGI, Eugene, OR, USA) with an appropriate size selected by measuring head circumference. In both datasets electrode impedances were maintained below 50 k Ω during recording and the EEG signal was referenced to the vertex. A bandpass filter of 0.1 to 100 Hz and an amplifier gain of 10,000 was used by both datasets. Control data was sampled at a rate of 500 Hz and data for those with DS was sampled at a rate of 250 Hz.

In terms of differences in EC paradigm between groups, the TD group were instructed to close their eyes and open them again after a period of time, with this procedure then repeated multiple times. An identical procedure was used for 14 adults with DS;

however 11 individuals with DS instead had a continuous 5.5 minute block of EC recording (see Chapter 3 General Methods for more information).

Further identifiable differences in protocol methods were that the research assistant voice in the control dataset was recorded whereas in this study the voice was not recorded. Additionally, for the control dataset each EC recording lasted 40-seconds and was repeated 5 times, whereas in this study each EC recording lasted 30-seconds and was repeated 11 times. The shorter duration used for adults with DS minimised the likelihood participants falling asleep and allowed the researcher to remind the participant of the task instructions, and the greater number of overall blocks ensured a sufficient amount of useable data was collected from each participant.

5.2.3 EEG processing and analysis

All EEG pre-processing and analysis steps were identical for both groups (see Chapter 3 General Methods for more information). Pre-processing was conducted with MATLAB software installed with an EEGLAB toolbox and additional ERPLAB plug-in (Delorme & Makeig, 2004; Lopez- Calderon & Luck, 2014). Analysis was carried out with MATLAB software using customised scripts to obtain absolute and relative power measures for each frequency band of interest (delta 0.5 – 4 Hz; theta 4 – 8 Hz; alpha 8 – 13 Hz; beta 13 – 30 Hz) for each region (frontal and occipital) for each individual. Additionally, alpha peak features were calculated (peak amplitude within the 8-13 Hz range and the frequency of this peak).

Specifically, absolute power-frequency measures were obtained through decomposition of the time-frequency signal using wavelet analysis. This was performed on non-overlapping 2-second epochs (≥ 12) for every channel. These were then averaged across all epochs, yielding a power-frequency spectrum for every electrode within each individual. Relative power measures were obtained for every electrode within each individual by dividing absolute power-frequency values by their total absolute power across the EEG spectrum (0.1- 30 Hz). Electrode montage averages were then used to obtain a measure of occipital (E70, E71, E74, E75, E76, E82, E83) and frontal (E4, E5, E10, E11, E12, E16, E18, E19) activity for each individual (See Figure 5.1).

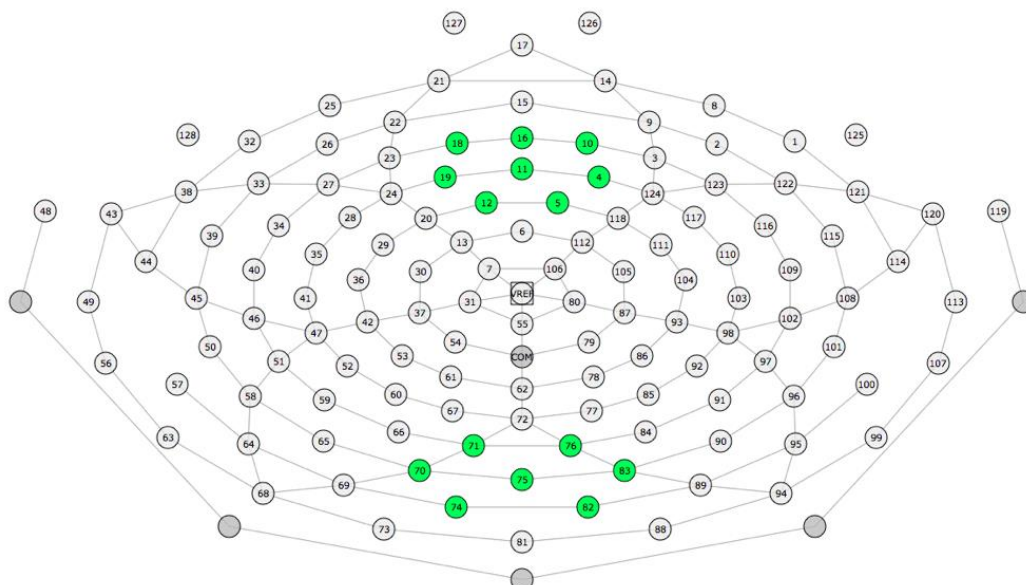


Figure 5.1 Electrode map illustrating occipital and frontal montages

Electrode map illustrating individual cap electrodes for occipital (bottom cluster; 70, 71, 74, 75, 76, 82, 83) and frontal (top cluster; 4, 5, 10, 11, 12, 16, 18, 19) montage averages used within this analysis.

5.2.4 Statistics and visualisation

Customised MATLAB scripts were used to produce power-frequency spectrum plots. All statistical analysis was performed with SPSS. Once each EEG variable had been calculated for every participant, data was screened for significant outliers (defined as > 3 SD from the group mean). Histograms were used to assess the normality of distribution for each variable and Levene's statistic was used to assess equality of variances.

In order to determine whether the variation in EC paradigm within individuals with DS influenced results, independent sample t-tests were used to compare absolute and relative power values between participants completing a full-block ($n=11$) and those completing a split-block ($n=14$) paradigm. As one t-test was significant, EC paradigm was added as a covariate for all comparisons when activity was compared between groups. All control participants were assigned to the split-block protocol. ANOCOVAs were used to statistically compare differences between groups. This was performed for each EEG variable at each region (occipital and frontal), using both absolute and relative power values. Alpha peak frequency values, however, were only analysed for absolute spectra as absolute and relative values were the same. Where the covariate (EC paradigm) was significant this was left in the model, and where not significant the

covariate was removed from the model. Partial eta squared values for each variable were used to provide an indication of effect size.

5.3 Results

5.3.1 Preliminary analysis

As detailed in the methods section of this chapter, EEG variables were screened for significant outliers (defined as > 3 SD from the mean) and participants with an outlier in any EEG variable were excluded. One control participant had an alpha peak frequency more than 3 SD from the mean and so they were removed from further analysis. Their matched participant with DS was also excluded at this stage. Final analysis contained 25 individuals in each group. Table 5.1 shows the demographics of all participants included in the final analysis. All variables appeared normally distributed according to histogram shape.

Group	n	Mean age (SD)	Age range	Sex
DS	25	27.76 (8.45)	17 – 44	12 M; 13 F
Control	25	27.68 (8.34)	16 – 44	14 M; 11 F

Table 5.1 Participant demographics for each group

Participant demographics of each group. Participants were match individually for age (within 1 year) and on a group-level for sex (groups were age 16-25 years, 26-35 years, 36 years and over). Ages are given in years.

Comparing those with full-block and split-block (n=14) paradigms, one t-test was statistically significant: there was significantly higher relative theta power in the frontal region of individuals with DS completing the full-block paradigm (M = .26 (0.2 SD)) compared to those completing the split-block paradigm (M = .25 (0.1 SD)), (t(14.96) = 2.35, p = .033 (.001; .023 95% CI)).

5.3.2 EEG variables within DS and control groups

Table 5.2 details absolute and relative values for each EEG variable in each region, within each group. Standard deviations in the DS group appear to be higher than those in the control group, particularly for peak frequency, indicative of more variability. Figure 5.2 (DS group spectra) and Figure 5.3 (control group spectra) further illustrate increased variability within the DS group, apparent from individual plotted spectra.

EEG measure (n= 25 per group)	Control mean (SD)		DS mean (SD)	
	Occipital	Frontal	Occipital	Frontal
Absolute delta power (0.5-4 Hz range; log μV^2)	5.41 (.36)	5.75 (.39)	5.71 (.52)	6.23 (.59)
Relative delta power (0.5-4 Hz range; log μV^2)	.37 (.02)	.37 (.02)	.39 (.02)	.39 (.02)
Absolute theta power (4-8 Hz range; log μV^2)	4.89 (.44)	5.15 (.34)	5.29 (.71)	5.69 (.65)
Relative theta power (4-8 Hz range; log μV^2)	.24 (.01)	.24 (.01)	.25 (.01)	.26 (.01)
Absolute alpha power (8-13 Hz range; log μV^2)	5.76 (.88)	5.82 (.85)	5.19 (.91)	5.43 (.96)
Relative alpha power (8-13 Hz range; log μV^2)	.19 (.02)	.16 (.01)	.15 (.02)	.15 (.02)
Absolute beta power (13-30 Hz range; log μV^2)	3.56 (.45)	3.64 (.46)	3.27 (.52)	3.46 (.54)
Relative beta power (13-30 Hz range; log μV^2)	.20 (.01)	.20 (.01)	.19 (.02)	.19 (.02)
Absolute peak amplitude (8-13 Hz range; log μV^2)	.24 (.08)	.23 (.09)	.11 (.06)	.12 (.06)
Relative peak amplitude (8-13 Hz range; log μV^2)	.03 (.00)	.03 (.00)	.03 (.00)	.03 (.00)
Absolute peak frequency (8-13 Hz range; Hz)	10.27 (.14)	10.30 (.21)	10.32 (1.07)	10.44 (1.11)

Table 5.2 EEG values for each group

Mean (SD) values for all EEG variables investigated, shown for each group and each region (occipital and frontal).

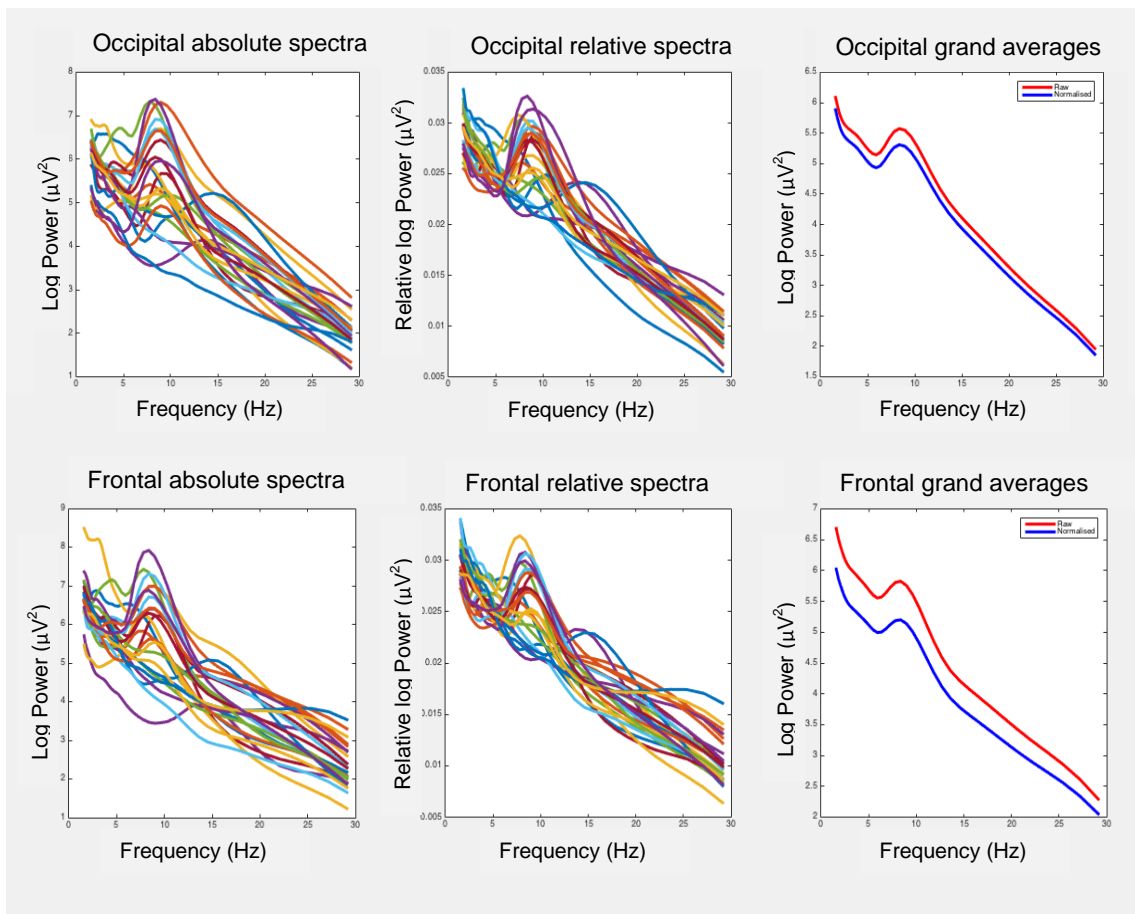


Figure 5.2 DS power-frequency spectra

DS group power-frequency spectra for occipital (top) and frontal (bottom) regions. Absolute and relative values are shown for each individual, in addition to absolute (red) and relative (blue) grand averages. Grand average y axis scale corresponds to absolute values (relative value grand average y axis scale not shown).

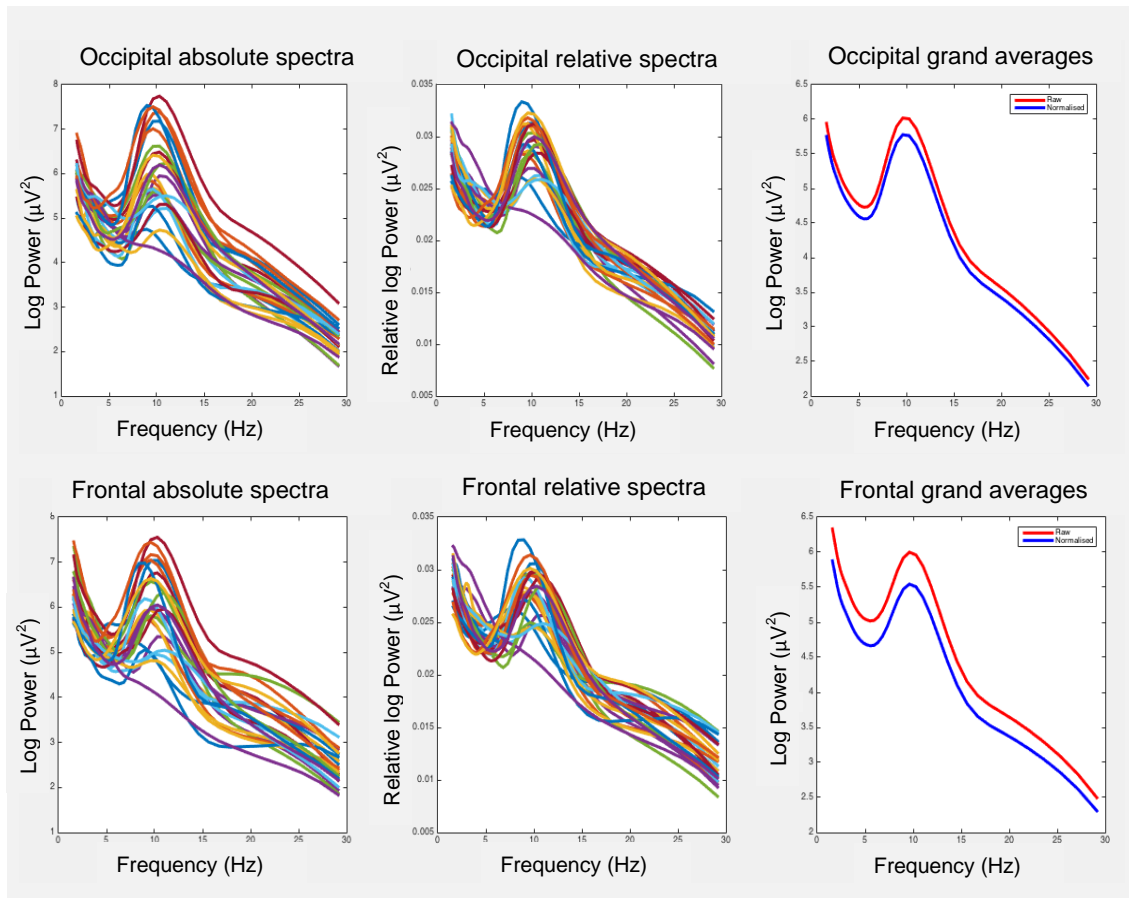


Figure 5.3 Control power-frequency spectra

Control group power-frequency spectra for occipital (top) and frontal (bottom) regions. Absolute and relative values are shown for each individual, in addition to absolute (red) and relative (blue) grand averages. Grand average y axis scale corresponds to absolute values (relative value grand average y axis scale not shown).

5.3.3 Statistical comparison of EEG variables between DS and control groups

The overall group differences in the power-frequency spectrum between DS and control participants are illustrated by Figure 5.4.

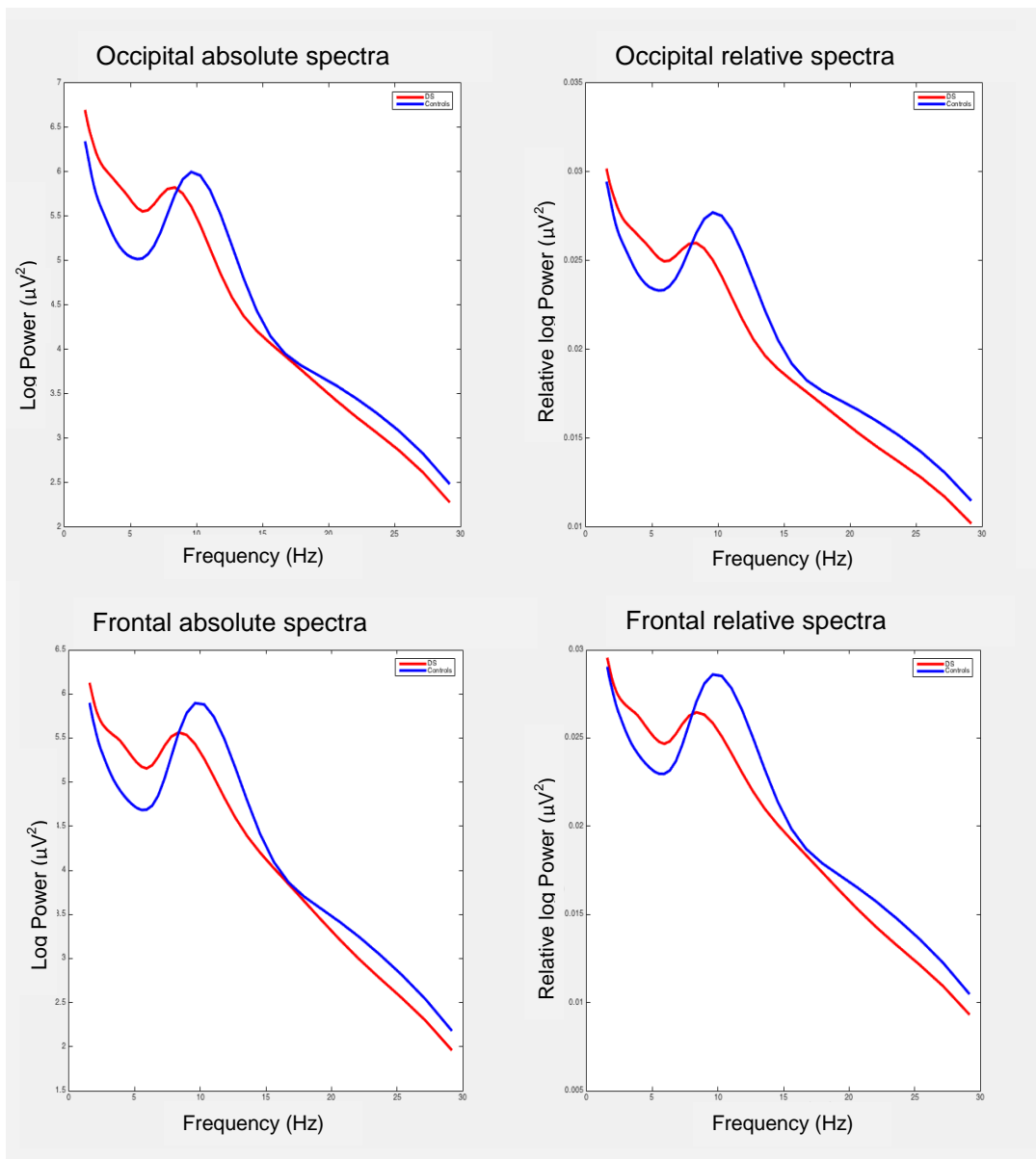


Figure 5.4 Group comparison of power-frequency spectra

Comparison between DS group (red) and control group (blue) grand average power-frequency spectra for occipital (top) and frontal (bottom) regions. Absolute (left) and relative (right) spectra both shown.

5.3.3.1 Occipital region analysis

Statistical analysis of EEG variables from the occipital region revealed significantly higher absolute and relative power in delta and theta bands (relative theta only; absolute theta not significant), and significantly lower absolute and relative power in alpha and beta bands, for those with DS compared to controls (see Figure 5.4 and Table 5.3). Those with DS also showed a significantly lower alpha peak amplitude. The effect sizes were greatest for relative alpha power, with group accounting for 56.5% of variance.

Additionally, in the occipital region EC paradigm had a significant effect on theta power, with both absolute and relative theta values higher for the full-block compared to the split-block paradigm (absolute values $5.57 \log \mu V^2$ (.63 SD) full-block and $5.08 \log \mu V^2$ (.71 SD) split-block; relative values $.26 \log \mu V^2$ (.02 SD) full-block and $.25 \log \mu V^2$ (.01 SD) split block). The only other EEG measure in this region for which EC paradigm had a significant effect was alpha peak frequency. Alpha peak frequency did not significantly differ between groups ($p=.224$) but there was a significant relationship between this measure and the EC paradigm covariate ($p=.009$): participants with DS completing the full-block paradigm had a significantly higher occipital alpha peak frequency (10.76 Hz (1.27 SD)) compared to participants with DS completing the split-block paradigm (9.98 Hz (.76 SD)). It is noteworthy that participants completing the full-block also had higher standard deviation of peak frequency (1.27 vs .76), indicating more variability in this particular measure.

EEG measure (n= 25 per group)	Occipital	
	Equation	Partial eta squared
Absolute delta power (0.5-4 Hz range; $\log \mu V^2$)	$F(1, 47) = 1.91, p = .037^*$.039 group
Relative delta power (0.5-4 Hz range; $\log \mu V^2$)	$F(1, 47) = 8.18, p = .006^{**}$.148 group
Absolute theta power (4-8 Hz range; $\log \mu V^2$)	² Group: $F(1, 47) = .94, p = .338$; Paradigm: $F(1, 47) = 4.73, p = .035^*$.020 group; .091 paradigm
Relative theta power (4-8 Hz range; $\log \mu V^2$)	¹ Group: $F(1, 47) = 13.98, p = .001^{***}$; Paradigm: $F(1, 47) = 6.77, p = .012^*$.229 group; .126 paradigm
Absolute alpha power (8-13 Hz range; $\log \mu V^2$)	$F(1, 47) = 5.20, p = .027^*$.100 group
Relative alpha power (8-13 Hz range; $\log \mu V^2$)	$F(1, 47) = 61.04, p \leq .000^{***}$.565 group
Absolute beta power (13-30 Hz range; $\log \mu V^2$)	$F(1, 47) = 4.03, p = .050^*$.079 group
Relative beta power (13-30 Hz range; $\log \mu V^2$)	$F(1, 47) = 8.32, p = .006^{**}$.150 group
Absolute peak amplitude (8-13 Hz range; $\log \mu V^2$)	$F(1, 47) = 27.88, p \leq .000^{***}$.372 group
Relative peak amplitude (8-13 Hz range; $\log \mu V^2$)	$F(1, 47) = 9.72, p = .003^{**}$.171 group
Absolute peak frequency (8-13 Hz range; Hz)	² Group: $F(1, 47) = 1.52, p = .224$; Paradigm: $F(1, 47) = 7.38, p = .009^{**}$.031 group; .136 paradigm

Table 5.3 Occipital region group comparison

Results of ANCOVAs between groups for each EEG variable for occipital region. ¹Where the covariate (EC paradigm) is significant both models are reported. ²Where only the covariate is significant (group not significant) both models are reported. Asterisk used to denote significance level ($\leq .05^*$, $\leq .01^{**}$, $\leq .001^{***}$). Effect sizes of significant model variables illustrated with partial eta squared value.

5.3.3.2 Frontal region analysis

Results for the frontal region followed the same pattern (see Table 4). Statistical analysis of EEG variables from the frontal region revealed that all group differences (including both absolute and relative values) were statistically significant, apart from alpha peak frequency ($p = .664$) in addition to absolute alpha and beta power ($p = .179$; $p = .569$ respectively). Overall absolute and relative delta and theta power values were significantly higher in individuals with DS, whereas relative alpha and beta power values were significantly lower (including absolute and relative alpha peak amplitude).

The effect sizes were greatest for absolute alpha peak amplitude and relative alpha power, with group accounting for 28.8% and 20.9% of variance in these variables respectively. Additionally, EC paradigm had a significant effect on relative theta power in this region ($p = .007$; explaining an additional 14.3% in variance), with higher values for the full-block compared to the split-block paradigm (.26 log μV^2 (.02 SD) full-block; .24 log μV^2 (.01 SD) split block).

EEG measure (n= 25 per group)	Frontal	
	Equation	Partial eta squared
Absolute delta power (0.5-4 Hz range; log μV^2)	F(1, 47) = 11.14, p = .002**	.192 group
Relative delta power (0.5-4 Hz range; log μV^2)	F(1, 47) = 8.34, p = .006**	.151 group
Absolute theta power (4-8 Hz range; log μV^2)	F(1, 47) = 6.78, p = .012*	.126 group
Relative theta power (4-8 Hz range; log μV^2)	¹ Group: F(1, 47) = 9.25, p = .004**; Paradigm: F(1, 47) = 7.83, p = .007**	.164 group; .143 paradigm
Absolute alpha power (8-13 Hz range; log μV^2)	F(1, 47) = 1.87, p = .179	.038 group
Relative alpha power (8-13 Hz range; log μV^2)	F(1, 47) = 12.45, p \leq .001***	.209 group
Absolute beta power (13-30 Hz range; log μV^2)	F(1, 47) = .329, p = .569	.007 group
Relative beta power (13-30 Hz range; log μV^2)	F(1, 47) = 4.45, p = .040*	.087 group
Absolute peak amplitude (8-13 Hz range; log μV^2)	F(1, 47) = 19.05, p \leq .000***	.288 group
Relative peak amplitude	F(1, 47) = 8.98, p = .004**	.160 group

(8-13 Hz range; log μV^2)		
Absolute peak frequency (8-13 Hz range; Hz)	F(1, 47) = .191, p = .664	.004 group

Table 5.4 Frontal region group comparison

Results of ANCOVAs between groups for each EEG variable for frontal region. ¹Where the covariate (EC paradigm) is significant both models are reported. Asterisk used to denote significance level ($\leq .05^*$, $\leq .01^{**}$, $\leq .001^{***}$). Effect sizes of significant model variables illustrated with partial eta squared value.

5.3.3.3 Adjusted p-value analysis

The above analysis details the results of 22 statistical tests. Due to the exploratory nature of this investigation, p-values have not been adjusted to correct for multiple comparisons. Using a Bonferroni correction (p-values are divided by the number of comparisons; adjusted p-value $\leq .002$), the following EEG measures would remain significantly different between groups:

- Occipital Relative theta power
- Occipital relative alpha power
- Occipital absolute alpha peak amplitude
- Frontal absolute delta power
- Frontal relative alpha power
- Frontal absolute alpha peak amplitude

5.4 Discussion

5.4.1 Summary of findings

This chapter aimed to determine EEG differences between adults with DS and TD age- and sex- matched controls. The analysis here has shown that for this sample of adults with DS, delta and theta power values are significantly higher whereas alpha and beta power values are significantly lower compared to age- and sex- matched control subjects. Results provide evidence for specific hypotheses related to delta, theta and alpha power. Beta activity, however, was hypothesised to have more power in individuals with DS, but less power was found. Overall these results are indicative of a slower EEG spectrum in individuals with DS compared to matched TD controls, with

significantly more power in slower frequencies and significantly less power in mid-to-faster frequencies.

The pattern of findings observed is true for both occipital and frontal regions. This is in line with original hypotheses. In frontal regions, however, differences in absolute values of alpha and beta power (although still lower in DS) were not significant. A secondary aim of this chapter was to determine if between-group comparisons differed for power results obtained from absolute and relative values. It was hypothesised regions investigated and measures used would not yield different results. Although group differences for absolute and relative values did not differ substantially, effect sizes were generally larger for relative values. This is likely due to normalisation of the values (ensuring each value is relative to each individuals' total EEG activity) having the effect of reducing variability in the sample, and consequently increasing statistical power. Due to the high degree of variability in individuals with DS, with larger SD values compared to the control group, utilising relative values may therefore be particularly beneficial in this population.

According to effect sizes, the most strongly associated EEG characteristics with group in both regions were those relating to alpha activity (relative alpha power in occipital and relative alpha power in addition to absolute alpha peak amplitude in frontal). Interestingly alpha peak frequency was not significantly associated with group in either region but was significantly associated with EC paradigm in the frontal region, with participants with DS who had undergone a full-block paradigm having a faster peak by approximately 0.8 Hz compared to participants with DS who had the split-block protocol. EC paradigm was also associated with significantly more occipital (absolute and relative) and frontal (relative only) theta power in the full-block compared to split-block protocol.

In terms of regional differences, although the pattern of activity did not differ between the two regions investigated, some absolute measures that reached significance in occipital regions failed to reach significance for frontal regions (the effect of group on absolute alpha power and absolute beta power, and the effect of paradigm on absolute theta power). Participants with DS had larger SD values in frontal regions compared to occipital regions for all these absolute variables, and so this may have affected statistical power here. Alternatively, the effect of group may be smaller for these variables in frontal regions. This is evidenced by stronger effect sizes in occipital regions compared to frontal regions when relative alpha power and relative beta power

are examined (56.5% occipital vs 20.9% frontal effect size for relative alpha power; 15.0% occipital vs 8.7% frontal effect size for relative beta power).

5.4.2 Research in context

As discussed previously, differences in alpha band activity between individuals with DS and TD controls have tended to be the most commonly reported finding in the literature. This is in keeping with the findings of this study, in that the effect of group was strongest for alpha band characteristics (power and peak amplitude). Also in keeping with the findings of this study, a number of other studies have reported no effect of group on alpha peak frequency (Politoff et al., 1996; Babiloni et al., 2010). However, the difference in peak frequency variability (SD) in individuals with DS compared to controls is large (.14 Hz SD in controls compared to 1.07 Hz SD in DS), which may have impacted statistical power. It is unclear whether these differences in variability also exist within-individuals (i.e. whether individuals with DS have an unstable peak frequency). Furthermore, paradigm effects significantly influenced occipital alpha peak frequency in this sample, and so the sensitivity of alpha peak frequency to small differences in EC protocol may go some way to explaining the inconsistencies within the literature regarding this measure (with some studies reporting a slower frequency in individuals with DS; Ono et al., 1992; Soinenen et al., 1993; Murata et al., 1994; Locatelli et al., 1996; Velikova et al., 2011).

Overall when examining previous literature the findings of this study are consistent with many previous studies: higher delta activity (Locatelli et al., 1996; Partanen, et al., 1996; Politoff et al., 1996; Medaglini et al. 1997; Babiloni et al., 2009; Babiloni et al., 2010; Velikova et al., 2011), higher theta activity (Ono, 1993; Murata et al., 1994; Locatelli et al., 1996; Partanen, et al., 1996; Politoff et al., 1996; Medaglini et al. 1997; Babiloni et al., 2009; Babiloni et al., 2010; Velikova et al., 2011), lower alpha activity (Babiloni et al., 2009; Medaglini et al. 1996; Locatelli et al., 1996), and lower beta activity (Babiloni et al. (2009, 2010)) in DS have previously been reported. The same pattern of activity in terms of similar results for absolute and relative values has also previously been reported by studies utilising both measures (Locatelli et al., 1996; Medaglini et al., 1996).

Previous studies into regional differences in EEG activity between individuals with DS compared to controls have also tended to report that differences in alpha and beta activity between groups may be most apparent in posterior regions (Medaglini et al. 1997; Locatelli et al., 1996). Furthermore, stronger effect sizes for delta activity in

frontal compared to occipital regions were found in this study, which is also in keeping with previous literature (Babiloni et al 2009; Medaglini et al.1997; Locatelli et al.,1996). Strongest effects in the literature for theta power tend to be in central regions (Medaglini et al.1997; Locatelli et al.,1996), which have not been examined in this study.

It is likely that splitting the EC recording block reduced drowsiness of participants, as intended. This is evidenced by theta power – a measure that is increased with light drowsiness (Britton et al., 2016) – being significantly increased in participants with DS who underwent the full-block paradigm. Mechanisms underlying the relationship between EC paradigm and occipital alpha peak frequency also found here are less clear (higher alpha peak frequency associated with full-block protocol). Although it is reported that drowsiness can also influence alpha band oscillations (Gennaro et al., 2001; Putilov & Arcady et al., 2012), and so again this relationship may be due to differing levels of drowsiness between paradigms.

There is evidence to suggest that the key findings of this chapter – that individuals with DS may have more power in slower frequencies and less power in mid-to-faster frequencies compared to TD individuals – may be related to cognitive impairment. In particular previous research has shown that in the TD population, increased delta and reduced alpha activity have been associated with poorer memory performance (Babiloni et al., 2007). It has also been demonstrated in the TD population that individuals with mild cognitive impairment (MCI) have increased delta and theta activity and decreased alpha activity compared to healthy controls (Guner et al., 2017; Gouw et al. 2017). Furthermore research suggests these spectral differences, in addition to reductions in beta power, become more pronounced with progression from MCI to AD (Hsiao et al, 2013; Scrascia et al. 2014). It is therefore possible the differences between individuals with DS and TD controls detailed in this chapter may be related to the presence of ID or AD-neuropathology in individuals with DS, or a combination of these two factors.

At present the contribution of these factors and their underlying mechanisms are unclear. It is likely, however, that atypical or delayed maturation plays an important role. In particular, studies examining EEG changes that take place during brain maturation in the TD population have reported age-related reductions in delta and theta power and age-related increases in alpha and beta power between ages 10 and 13 years (Cragg et al, 2011). As the mean age of participants in this study is 27 years – which is prior to when significant amyloid-burden is expected in adults with DS (Mann,

1988) – maturational atypicalities may be the most likely explanation. Studies examining different age groups are necessary to elucidate this further.

5.4.3 Limitations, strengths and future research

A particular strength of this study is that EEG measurements utilised were not limited to the occipital region. Examining both occipital and frontal areas indicates that group differences are likely to be widespread. Nevertheless conclusions cannot be drawn about other regions (central, parietal or temporal), and it is possible group differences in other regions do not follow the same pattern in occipital and frontal areas. Alternative analysis methods are available that may be more appropriate for scalp-wide analysis of EEG group differences (for example statistical parametric mapping; Kiebel et al., 2005). Future studies may benefit from using such approaches in order to fully explore regional differences across the whole scalp.

An additional strength of this study is that EEG differences between groups were examined with both absolute and relative values. As mentioned previously, “normalising” EEG power in each band relative to an individual’s total EEG power helps to account for individual differences in broadband power. This has the beneficial effect of reducing the influence of potential morphological and anatomical differences between subjects; for instance an individual with a larger brain may have more power in all bands. Expressing power as a relative value therefore improves the ability to compare group data from participants that have a high degree of inter-individual variability in brain anatomy, as in the population with DS. Furthermore, peak frequency measures were obtained from all participants by removing the individual linear trend from the EEG spectrum to achieve “spectral normalisation”. This method has not been utilised in DS studies previously but is particularly useful in this population due to many individuals having a small peak that is not measurable beyond the natural $1/f$ background EEG noise. It could therefore be argued that the peak frequency measures reported here are more valid than those reported within previous literature for this population. Nevertheless, due to the significant impact of EC protocol on this measure, conclusions regarding alpha peak frequency in this study should still be taken with caution.

Although variation in EC protocol between individuals with DS is a limitation of this study, its effects have been controlled for by including this as a covariate during analysis. It has also provided useful information pertaining to the most appropriate design for these studies in this population, which was a secondary aim of this thesis.

Results suggest that splitting the recording block into smaller segments may have reduced drowsiness, and so it is recommended that future studies use this approach.

This study benefitted from only including individuals with genetically confirmed trisomy 21 and the exclusion of individuals with noticeable cognitive decline or a diagnosis of dementia. This ensured results were not influenced by any individuals with a rarer form of DS (for example mosaicism where it is likely not all neuronal cells have three copies of chromosome 21), and results are valid for individuals with DS prior to dementia onset. These variables are not commonly controlled for within DS studies, despite them substantially improving the validity and generalisability of findings.

As with any study comparing two datasets collected in different EEG laboratories, differences in data acquisition may have influenced findings. For example, a recorded voice as opposed to a live researcher giving instructions may cause differences in participant motivation between groups. It is unclear in what way such factors may have influenced the group differences reported in this study. Qualitatively the data was the same in both groups (EC resting-state) and so it is unlikely small differences in protocol would have influenced overall conclusions. Additionally, the findings reported here are fairly robust (many p values $<.01$), were confirmed in two distant brain regions, and most were significant for both absolute and relative power values.

Utilising open-source datasets is beneficial for allowing small exploratory studies of clinical populations access to a large control cohort in order to obtain closely matched control subjects, and reduce costs, and burden on research participants. The current study here achieved age-matching on an individual basis and sex-matching on a group basis. Close age-matching is particularly important in this population due to the delayed maturational and accelerated ageing aspects of DS, and so this is a particular strength of the study.

A further consideration of this study is that only EC resting-state activity was examined. It is therefore problematic to generalise findings beyond this specific task and to make conclusions about overall differences in brain activity between individuals with DS and TD controls. This study would have benefitted from using comparable EO resting-state data to make additional group comparisons for more in-depth investigation. Future studies should incorporate this.

It should be noted that the sample size for this study is relatively small ($n = 25$ per group). It is possible that this has impacted on the ability to detect significant

differences between groups. For example, the group difference in alpha peak frequency (see Figure 5.4) did not reach statistical significance in this study, but may have done so in a larger sample.

An additional consideration is that although there was an age range of 16 to 44 years in this study, the mean age of the sample was relatively young (28 years). The ability to generalise conclusions beyond young adults with DS is therefore limited. As mentioned previously, it is necessary to examine different age groups to determine potential underlying mechanisms of the group differences in EEG activity reported here. Longitudinal studies targeted at children, young adults and older adults (aged over 35 years) would also further enable maturational and ageing influences to be fully examined.

Future studies may benefit from the examination of gamma band activity. Gamma activity is commonly filtered out in human EEG studies due to muscle artifacts and mains power interference sharing gamma frequencies. As significant differences between groups have been reported in all bands investigated it is possible gamma activity would also differ between the groups. Further studies, ideally with data acquired from electrically shielded laboratories to eliminate noise from mains power lines, are necessary to investigate this.

5.4.4 Conclusions

The analysis within this chapter suggests that during EC resting state EEG recordings, individuals with DS have an overall slower EEG spectrum compared to matched TD control subjects. Alpha band in particular shows strong group differences, with power reduced in DS. Also illustrated is the utility of analysing topographical differences, of using absolute as well as relative power values, and the importance of carefully considering EC protocols (with split-block paradigms potentially reducing drowsiness). It remains to be determined, however, whether observed differences occur in brain regions not investigated here, and whether differences are stable across the lifespan or are instead associated with the dynamic processes of either cerebral maturation or ageing in DS. Exploring individual differences in EEG variables within the DS population will help elucidate any relationships between these variables and age and/or cognitive ability. This will be the focus of the following two experimental chapters.

Chapter 6 Within Down syndrome EEG correlates of general cognitive ability

6.1 Introduction

This chapter will focus on individual differences in EEG activity between adults with DS, using both EO and EC resting-state EEG data. Measures of interest will be correlated with a measure of general cognitive ability (raw KBIT-2 score) to ascertain how individual EEG differences may relate to general cognitive ability in this population.

Methods within this chapter have been informed by findings of the previous chapter, which pertained to differences in EC resting-state activity between individuals with DS and TD controls. Specifically, analysing both occipital and frontal regions, and activity within all bands investigated (delta, theta, alpha and beta), was found to be informative. These methods will therefore be implemented within the current chapter. Previous studies examining the relationship between resting-state EEG characteristics and general cognitive ability within adults with DS have reported associations across the EEG spectrum. Differences in resting-state EEG power and frequency measures within individuals with DS and their relationships with cognitive abilities reported by previous studies are detailed within the literature review in section 2.4.

6.1.1 Frequency

Overall, results regarding alpha frequency are mixed, with some studies reporting positive associations with cognitive ability (Soininen et al., 1993; Locatelli et al., 1996; Velikova et al., 2011) and others reporting no significant associations (Ono et al., 1993; Politoff et al., 1996). There is, however, some evidence to suggest slowing of the alpha peak frequency may occur with the onset of AD in people with DS (Visser et al., 1996). This may therefore confound results regarding correlations with ability in studies where participants with dementia were not excluded (e.g. Velikova et al., 2011). The present study aims to overcome this issue by excluding individuals with evidence of cognitive decline or a diagnosis of dementia.

6.1.2 Power

In terms of power differences associated with cognitive ability within individuals with DS, it is difficult to ascertain which reported relationships are independent of cognitive decline and which may be confounded by this. Overall there is a suggestion that measures indicative of a slower EEG spectrum (i.e. more power in lower frequencies and less power in higher frequencies) are associated with lower cognitive ability. This is provided by the two studies investigating this that attempted to control for the presence of significant cognitive decline by either excluding individuals with evidence of decline (Politoff et al., 1996), or by analysing these individuals separately to individuals without detectable decline (Medaglini et al., 1997). There is also an indication in the TD literature that lower-alpha (typically 8-10 Hz) and upper-alpha (typically 10-13 Hz) bands have different roles in cognition (discussed in Chapter 2), with lower-alpha activity potentially indicative of attentional readiness and upper-alpha activity potentially reflecting the activity of memory systems. Studies analysing alpha as a single band may therefore lack the ability to detect significant relationships with cognitive ability. The present study aims to overcome this potential limitation by analysing lower-alpha and upper-alpha each as individual frequency bands.

Although utilising both absolute and relative EEG measures was found to be an informative approach in the previous chapter, statistical analysis within the current chapter will only use absolute values (both absolute and relative values will still be shown within EEG spectra figures, however, for illustrative purposes). This is due to the larger number of statistical tests within this chapter. Consequently, utilising relative values in addition to absolute would greatly increase the chance of a type 1 statistical error. As discussed in the previous chapter, three studies have explored resting-state activity in individuals with DS using both absolute and relative EEG values (Locatelli et al., 1996; Medaglini et al., 1996; Politoff et al., 1996). None of these studies reported any differences in associations using these different values.

6.1.3 Reactivity

The collection of both EO and EC resting-state data will enable the investigation of alpha reactivity to eye-opening (i.e. the EO/EC alpha power ratio; given as a percentage). Only one previous study has investigated this in individuals with DS and reported the EO/EC ratio was significantly associated with all neuropsychological measures investigated, with a higher ratio (i.e. larger percentage change between EC and EO activity) associated with better cognitive performance (Partanen et al., 1996). This measure will therefore be utilised within the current study.

6.1.4 Age-related change

It is of further relevance that in adults with DS age-related changes have been reported for power (Soininen et al., 1993; Murata et al., 1994; Locatelli et al., 1996), frequency (Ono et al., 1992; Soininen et al., 1993; Murata et al., 1994; Katada et al., 2000), and reactivity (Partanen et al., 1996) measures. Overall studies are indicative of slowing of the EEG spectrum and reduced reactivity with increasing age. Controlling for participant age within analysis is therefore necessary and will be implemented within this study. Age will also be considered in more depth in the analyses within this chapter.

Furthermore, as slowing of alpha rhythms are commonly reported in adults with DS, an extended-band approach (4-13 Hz) will be implemented for the investigation of alpha peak characteristics and alpha reactivity measures. The aim of this is to improve measurement accuracy by ensuring alpha activity and peaks that fall below 8 Hz are included for the purpose of these analyses. As discussed in section “2.2 Resting-state EEG”, alpha rhythms are known to operate across a wider frequency range than 8-13 Hz and there is substantial inter-individual variability regarding these limits (Haegens et al., 2014). Within previous DS literature, similar extended-band approaches have been utilised, including 7-14 Hz (Kreezer, 1939), 6-14 Hz (Ellingson & Lathrop, 1973), 4-14 Hz (Soininen et al., 1993), and 4-13 (Salem et al., 2015).

6.1.5 Aims and hypotheses

The primary aims of this chapter are to examine whether EEG activity is predicted by participant age and experimental variables (counterbalanced order and for EC paradigms whether the protocol was split-block or full-block), and whether KBIT-2 score is predicted by EEG activity. Significant predictors of EEG activity will be controlled for when exploring associations between EEG measures and KBIT-2 score. EEG measures to be investigated include EO and EC band power (delta, theta, lower-alpha, upper-alpha, and beta), in addition to peak amplitude, peak frequency, and reactivity in the extended-alpha range.

Investigating whether age or experimental variables are significant predictors of any EEG measures not only allows the effect of age on EEG measures to be examined but also enables the influence of any significant variables to be accounted for when associations between EEG measures and general cognitive ability are investigated. It will also be investigated whether any relationships with age are still present when older

adults (aged over 35) are excluded from analyses, in order to determine whether aging effects are likely to be associated with the development of neuropathology associated with AD in DS.

Based on previous DS literature indicating slowing of the EEG spectrum and reduced reactivity with age, it is hypothesised that:

- a) paradigm variables (order and EC paradigm) will not significantly influence any EEG measures;
- b) measures indicative of slowing (slower alpha peak frequency, more power in lower-frequencies (delta, theta and lower-alpha), less power in upper-frequencies (upper-alpha and beta) and reduced reactivity, will be associated with increasing age in EC measures (no significant relationships are expected for EO measures and age);
- c) for EEG measures which are significantly predicted by age, these will remain significant when adults over age 35 are removed from analyses.

In relation to cognitive ability, based on previous findings, it is hypothesised that:

- d) Lower KBIT-2 score will be associated with measures indicative of EEG slowing (slower alpha peak frequency and more power in lower-frequencies (delta, theta and lower-alpha)), reduced alpha reactivity, and reduced alpha peak amplitude;
- e) Due to a lack of previous literature investigating the relationship between EO resting-state activity and cognitive ability in individuals with DS, it is hypothesised there will be no relationships between any EO measures and KBIT-2 – all significant relationships are expected for the EC paradigm only (detailed above).

A secondary aim is to investigate whether findings differ between occipital and frontal regions. It is hypothesised that:

- f) significant relationships with slow waves (delta and theta activity) would be found in frontal regions only, whereas relationships with alpha activity would be in occipital regions only. No differences between regions were expected for any relationships with beta activity.

6.2 Methods

6.2.1 Participants

Participants with a clinical diagnosis of dementia (n=5) or evidence of possible cognitive decline (according to CAMDEX-DS assessment; n=9) were excluded from this stage of analysis. Further details on these criteria are provided in section “3.4 Cognitive Assessment”. Participants were also excluded if they had a form of DS other than trisomy 21 (partial trisomy (n=1) and translocation (n=1)), or if no genetic information had been obtained (n=1). All remaining participants able to complete one or both recording paradigms were included for analysis (n=48). KBIT-2 raw score was used to provide a measure of general cognitive ability (see section “3.4 Cognitive Assessment”). No participants included in this chapter had a partially completed KBIT-2, and so no scores were imputed.

The following is an explicit list of inclusion criteria for participants in this chapter:

- Sufficient data (≥ 12 2-second segments) was obtained from the participant during one or both recording paradigms
- Participant has genetically confirmed trisomy 21
- Participant did not show evidence of cognitive decline or have a diagnosis of dementia at the time of cognitive assessment

6.2.2 EEG analysis

See section “3.7.2 EEG measures” and section “5.2.3 EEG processing and analysis” for full details on EEG pre-processing and analysis methods. EEG analysis methods in this chapter are identical to those described in the previous chapter under “5.2.3 EEG processing and analysis”. However, within this chapter alpha activity was split into lower and upper bands (rationale discussed above in “6.1 Introduction”). Therefore, the following frequency bands of interest were analysed: delta 0.5 – 4 Hz; theta 4 – 8 Hz; low-alpha 8 – 10 Hz; upper-alpha 10 – 13 Hz; beta 13 – 30 Hz. Additionally within this chapter alpha peak features (amplitude and frequency) were calculated within the 4-13 Hz range (rationale discussed above in “6.1 Introduction”).

Furthermore, occipital alpha reactivity values were obtained for participants completing both recording paradigms (n=36). These were calculated on an individual basis

according to methods described by Partanen et al. (1996), by subtracting individual EC power (4-13 Hz range) from individual EO power in this range, divided by each individual's total EC power in this range and multiplied by 100 (% change):

$$\text{Equation: } 100((EC-EO)/EC)$$

Where individuals had a negative value (i.e. alpha activity was suppressed with eye-closure and increased with eye-opening; the opposite of what is considered typical alpha activity), participants were given a score of zero. In order to determine whether this approach was influencing results, analyses were also carried out with these individuals excluded (n=3). The same results were given by both approaches. Results from the original approach (assigning a reactivity score of zero to these participants) are described here (see Table 6.4).

6.2.3 Statistics and visualisation

Customised MATLAB scripts were used to produce power-frequency spectrum plots. All statistical analysis was performed with SPSS. Once each EEG measure had been calculated for every participant, data was screened for significant outliers (defined as > 3 SD from the group mean). Participants who had one EEG measure or more for which their data was considered an outlier were excluded from the analysis of those particular measures.

A two-step approach was taken to statistical analysis. First, multiple regression was used to examine predictors of each EEG measure. Predictors of EEG measures that were examined included age and experimental variables (counterbalanced order of paradigm and additionally for EC data whether the paradigm was split or full-block). Secondly, multiple regression was used to examine whether each EEG measure was a significant predictor of KBIT-2. Significant predictors of EEG activity in stage 1 were used as additional predictors in this second stage of analysis in order to account for predictors contributing to variability within each EEG measure. All analyses were carried out for both regions (except for alpha reactivity which was only analysed in the occipital region). R squared values are for the total variance explained by predictors, and are used to provide an indication of effect size.

6.3 Results

6.3.1 Participants

Table 6.1 shows the demographics of participants included in this chapter. All participants retained after exclusion criteria were applied completed the EO paradigm and, of these participants, 36 also completed the EC paradigm (no retained participants completed EC alone).

Paradigm	n	Mean age (SD)	Age range	Sex	KBIT-2 (raw)	KBIT-2 range
EC	36	30.92 (11.03 SD)	16 – 56	17M; 19F	54.83 (19.64 SD)	10 – 102
EO	48	30.02 (10.86 SD)	16 – 56	22M; 26F	54.67 (18.91 SD)	10 – 108

Table 6.1 Participant demographics

Participant demographics for each resting-state paradigm. All EC participants included in this stage of analysis also completed the EO paradigm. Age given in years.

Two different participants each had one EEG measure for which their data was considered an outlier; these were EC frontal delta and EO frontal alpha peak amplitude. Histograms were used to assess the normality of the distribution for each variable.

For the EO paradigm there were 13 individuals aged over 35 years, and for the EC paradigm there were 10. Sample sizes for analyses with these individuals excluded were therefore 35 and 26 (EO and EC respectively).

6.3.2 Eyes-open paradigm

6.3.2.1 EO power-frequency spectra

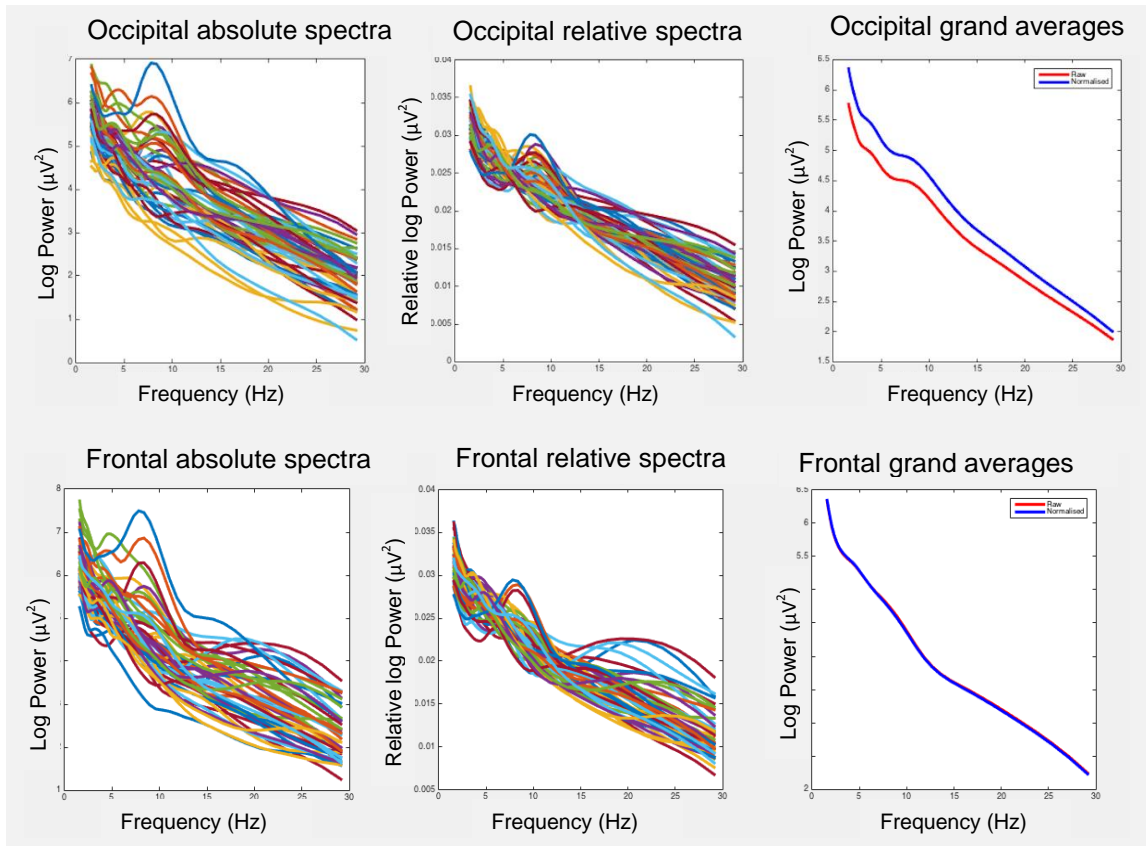


Figure 6.1 EO power-frequency spectra

EO power-frequency spectra for occipital (top) and frontal (bottom) regions. Absolute and relative values are shown for each individual, in addition to absolute (red; visibility mostly obscured by blue line in the frontal region) and relative (blue) grand averages. Grand average y axis scale corresponds to absolute values (relative value grand average y axis scale not shown).

6.3.2.2 EO paradigm: Occipital region results

Using EO data, multiple linear regressions were used to predict EEG measures (stage 1 analysis) for the occipital region (Table 6.2), based on variables of age and paradigm order. Multiple linear regressions were then used to predict raw KBIT-2 score based on each EEG measure, in addition to any significant predictors of the relevant measure in stage 1 (stage 2 analysis). In Table 6.2 both stages are shown in individual rows under each EEG measure (blue rows). Grey rows show results of multiple regressions with participants aged over 35 removed.

EO Occipital: Stage 1 analysis results

For the occipital region (Table 6.2 and Figure 6.2), age was a significant predictor of EEG activity in the alpha band, including both lower-alpha and upper-alpha power, in addition to alpha peak amplitude (positive relationship for all). No other EEG measures were significantly predicted by age in this region.

When participants over the age of 35 were excluded from analyses, only the relationship between age and alpha peak amplitude remained significant. Interestingly this relationship became stronger with the exclusion of these participants (R^2 of .097 increased to .157).

EO Occipital: Stage 2 analysis results

No variables investigated significantly predicted KBIT-2 in this region.

Eyes-open; Occipital (n=48)	M (SD)	Equation	Individual predictors	Unstandardised B (SE), Standardised B	Total R ²
Absolute delta power (0.5-4 Hz range) (log μV^2)	5.286 (.487)				
Outcome: Absolute delta power		F(2, 45) = .422, p= .658	Order: p= .823 Age: p= .432	.017 (.079), .033; -.005 (.007), -.122	.018
Outcome: KBIT-2		F(1, 46) = .265, p= .609	Delta: p= .609	2.942 (5.712), .076	.006
Absolute theta power (4-8 Hz range) (log μV^2)	4.642 (.585)				
Outcome: Absolute theta power		F(2, 45) = .218, p= .805	Order: p= .692 Age: p= .539	.028 (.095), .062; .005 (.008), .096	.010
Outcome: KBIT-2		F(1, 46) = .341, p= .562	Theta: p= .562	2.771 (4.749), .086	.007
Absolute lower-alpha power (8-10 Hz range) (log μV^2)	4.365 (.800)				
Outcome: Absolute lower-alpha power		F(2, 45) = 2.478, p= .095	Order: p= .330 Age: p= .033*	.122 (.124), .146; .024 (.011), .325	.099
Outcome: KBIT-2		F(2, 45) = .204, P= .817	Lower-alpha: p= .816 Age: p= .528	-.858 (3.658), -.036; .171 (.269), .098	.009
Outcome: Absolute lower-alpha power	4.310 (.850)	F(2, 32) = 2.042, p= .146	Order: p= .302 Age: p= .060	.169 (.161), .182; .045 (.023), .339	.113
Outcome: KBIT-2		F(1, 33) = .012, p= .913	Lower-alpha: p= .913	51.911 (17.420), .019	.000
Absolute upper-alpha power (10-13 Hz range) (log μV^2)	3.924 (.644)				
Outcome: Absolute upper-alpha power		F(2, 45) = 2.067, p= .138	Order: p= .688 Age: p= .049*	.041 (.101), .060; .018 (.009), .302	.084
Outcome: KBIT-2		F(2, 35) = .393, p= .677	Upper-alpha: p= .515 Age: p= .453	-2.969 (4.522), -.101; .203 (.268), .117	.017
Outcome: Absolute upper-alpha power	3.867 (.676)	F(2, 32) = .960, p= .394	Order: p= .684 Age: p= .175	.054 (.132), .073; .026 (.019), .248	.057
Outcome: KBIT-2		F(1, 33) = .719	Upper-alpha: p= .719	-1.808 (4.983), -.063	.004
Absolute beta power (13-30 Hz range) (log μV^2)	2.803 (.550)				
Outcome: Absolute beta power		F(2, 45) = 2.258 p= .116	Order: p= .720 Age: p= .064	-.031 (.086), -.054; .014 (.008), .282	.091
Outcome: KBIT-2		F(1, 46) = .269 p= .606	Beta: p= .606	-2.621 (5.050), -.076	.006
Absolute peak amplitude (4-13	.237				

Hz range; log μV^2	(.168)				
Outcome: Absolute peak amplitude		F(2, 45) = 2.417, p= .101	Order: p= .262 Age: p= .039*	.030 (.026), .168; .005 (.002), .316	.097
Outcome: KBIT-2		F(2, 45) = .184, p= .833	Peak amp: p= .902 Age: p = .593	2.143 (17.307), .019; .144 (.268), .083	.008
Outcome: Absolute peak amplitude	.233 (.178)	F(2, 32) = 3.029, p= .062	Order: p= .220 Age: p= .023*	.041 (.033), .211; .011 (.005), .403	.159
Outcome: KBIT-2		F(2, 32) = .703, p= .502	Peak amp: p= .834 Age: p = .314	4.249 (20.105), .039; .575 (.562), .189	.042
Absolute peak frequency (4-13 Hz range; log μV^2)	8.525 (2.395)				
Outcome: Absolute peak frequency		F(2, 45) = .124, p= .884	Order: p= .800 Age: p= .632	.100 (.391), .040; .017 (.034), .075	.005
Outcome: KBIT-2		F(1, 46) = .109, p= .743	Peak freq: p= .743	.383 (1.163), .049	.002

Table 6.2 EO occipital multiple regression power and alpha peak results

Multiple regression results for EEG power and alpha peak (4-13 Hz range) measures from EO recording condition (n=48) for occipital region. Grey rows show results of multiple regressions with participants aged over 35 removed (n=35 remaining). Asterisk used to denote significance level ($\leq .05^$, $\leq .01^{**}$, $\leq .001^{***}$). Effect sizes of each model are illustrated with R^2 value.*

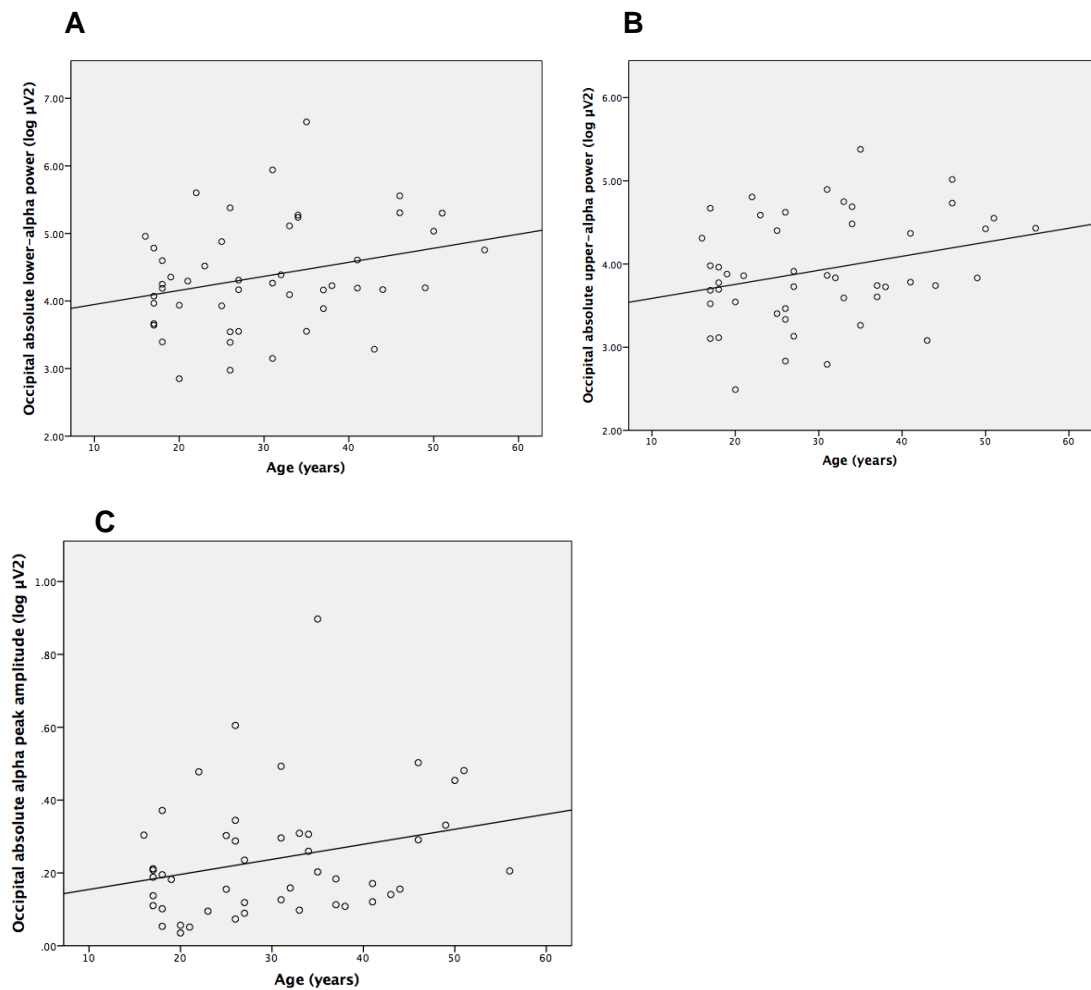


Figure 6.2 Panel of graphs showing significant relationships found for EO Occipital EEG data.

Scatter graphs show the significant positive relationship between age and lower-alpha power (A), upper-alpha power (B), absolute alpha peak amplitude (C). Data shown is for all participants ($n=48$). Regression lines shown.

6.3.2.3 EO paradigm: Frontal region results

Using EO data, multiple linear regressions were used to predict EEG measures (stage 1 analysis) for the frontal region (Table 6.3), based on variables of age and paradigm order. Multiple linear regressions were then used to predict raw KBIT-2 score based on each EEG measure, in addition to any significant predictors of the relevant measure in stage 1 (stage 2 analysis). In Table 6.3 both stages are shown in individual rows under each EEG measure (blue rows). Grey rows show results of multiple regressions with participants aged over 35 removed.

EO Frontal: Stage 1 analysis results

For the frontal region (Table 6.3 and Figure 6.3), age was a significant predictor of beta power (positive relationship). When participants over the age of 35 were excluded from analyses, this relationship no longer remained significant.

EO Frontal: Stage 2 analysis results

Delta power significantly predicted KBIT-2 in this region (see Figure 6.3B and Figure 6.4). Age was not a significant predictor of KBIT-2 in any regressions.

Eyes-open; Frontal (n=48)	M (SD)	Equation	Individual predictors	Unstandardised B (SE), Standardised B	Total R ²
Absolute delta power (0.5-4 Hz range) (log μV^2)	5.802 (.522)				
Outcome: Absolute delta power		F(2, 45) = 3.148, p= .053	Order: p= .259 Age: p= .079	.092 (.080), .167; -.013 (.007), -.263	.123
Outcome: KBIT-2		F(1, 46) = 4.625 p= .037*	Delta: p= .037*	10.943 (5.088), .302	.091
Absolute theta power (4-8 Hz range) (log μV^2)	5.129 (.582)				
Outcome: Absolute theta power		F(2, 45) = .192, p= .826	Order: p= .685 Age: p= .745	.039 (.095), .063; -.003 (.008), -.051	.008
Outcome: KBIT-2		F(1, 46) = 2.548, p= .117	Theta: p= .117	7.442 (4.663), .229	.052
Absolute lower-alpha power (8-10 Hz range) (log μV^2)	4.593 (.804)				
Outcome: Absolute lower-alpha power		F(2, 45) = .906 p= .411	Order: p= .353 Age: p= .238	.121 (.129), .143; .014 (.011), .183	.039
Outcome: KBIT-2		F(1, 46) = 1.211, p= .277	Lower-alpha: p= .277	3.765 (3.421), .160	.026
Absolute upper-alpha power (10-13 Hz range) (log μV^2)	4.075 (.607)				
Outcome: Absolute upper-alpha power		F(2, 45) = 1.316, p= .278	Order: p= .557 Age: p= .113	.057 (.096), .090; .014 (.008), .245	.055
Outcome: KBIT-2		F(1, 46) = 1.004, p= .321	Upper-alpha: p= .321	4.556 (4.546), .146	.021
Absolute beta power (13-30 Hz range) (log μV^2)	3.130 (.572)				
Outcome: Absolute beta power		F(2, 45) = 3.081 p= .056	Order: p= .728 Age: p= .018*	.031 (.088), .051; .019 (.008), .258	.120
Outcome: KBIT-2		F(2, 45) = .382 p= .685	Beta: p= .526 Age: p= .736	3.329 (5.204), .101; .093 (.274), .053	.017
Outcome: Absolute beta power	3.049 (.543)	F(2, 32) = 1.584, p= .221	Order: p= .967 Age: p= .099	-.004 (.104), -.007; .025 (.015), .298	.090
Outcome: KBIT-2		F(1, 33) = .134, p= .717	Beta: p= .717	2.266 (6.199), .064	.004
¹ Absolute peak amplitude (4-13 Hz range; log μV^2)	.222 (.152)				
Outcome: Absolute peak amplitude		F(2, 44) = .077, p= .926	Order: p= .995 Age: p= .709	.000 (.025), .001; .001 (.002), .059	.003
Outcome: KBIT-2		F(1, 45) = .696, p= .409	Peak amp: p= .409	15.547 (18.641), .123	.015
Absolute peak frequency (4-13 Hz range; log μV^2)	8.370 (2.242)				
Outcome: Absolute peak frequency		F(2, 45) = .345, p= .710	Order: p= .760 Age: p= .412	-.112 (.364), -.048; -.026 (.032), -.128	.015
Outcome: KBIT-2		F(1, 46) = .001 p= .980	Peak freq: p= .980	.031 (1.243), .004	.000

Table 6.3 EO Frontal multiple regression power and alpha peak results

Multiple regression results for EEG power and alpha peak (4-13 Hz range) measures from EO recording condition ($n=48$) for frontal region. Grey rows show results of multiple regressions with participants aged over 35 removed ($n=35$ remaining). ¹ Denotes an outlier was removed from this EEG measure. Asterisk used to denote significance level ($\leq .05^*$, $\leq .01^{**}$, $\leq .001^{***}$). Effect sizes of each model are illustrated with R^2 value.

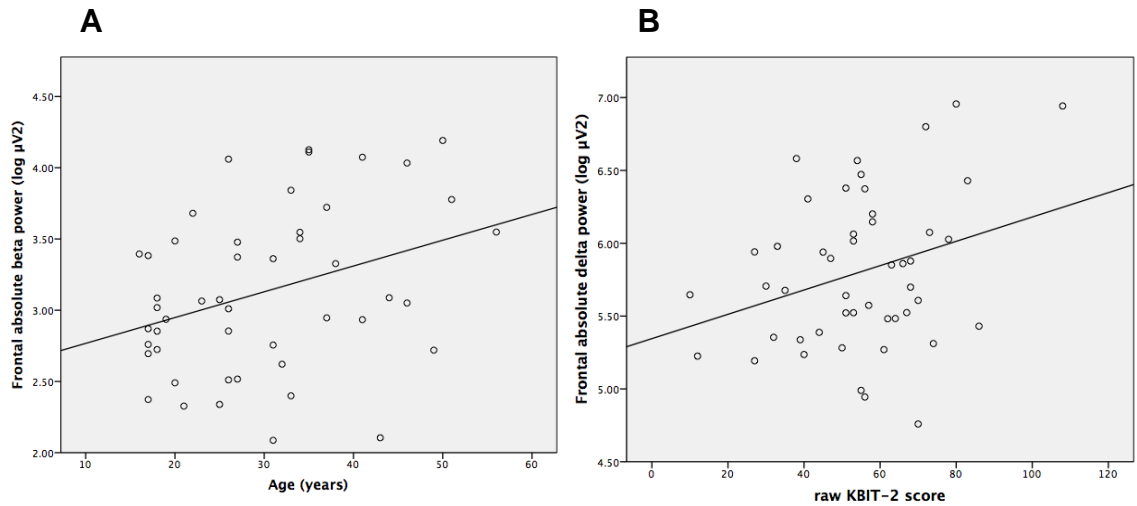


Figure 6.3 Panel of graphs showing significant relationships found for EO Frontal EEG data.

Scatter graphs show the significant positive relationship between age and absolute beta power (A) in the frontal region. Graph F shows the significant positive relationship between raw KBIT-2 score and absolute delta power in this region. Data shown is for all participants ($n=48$). Regression lines shown.

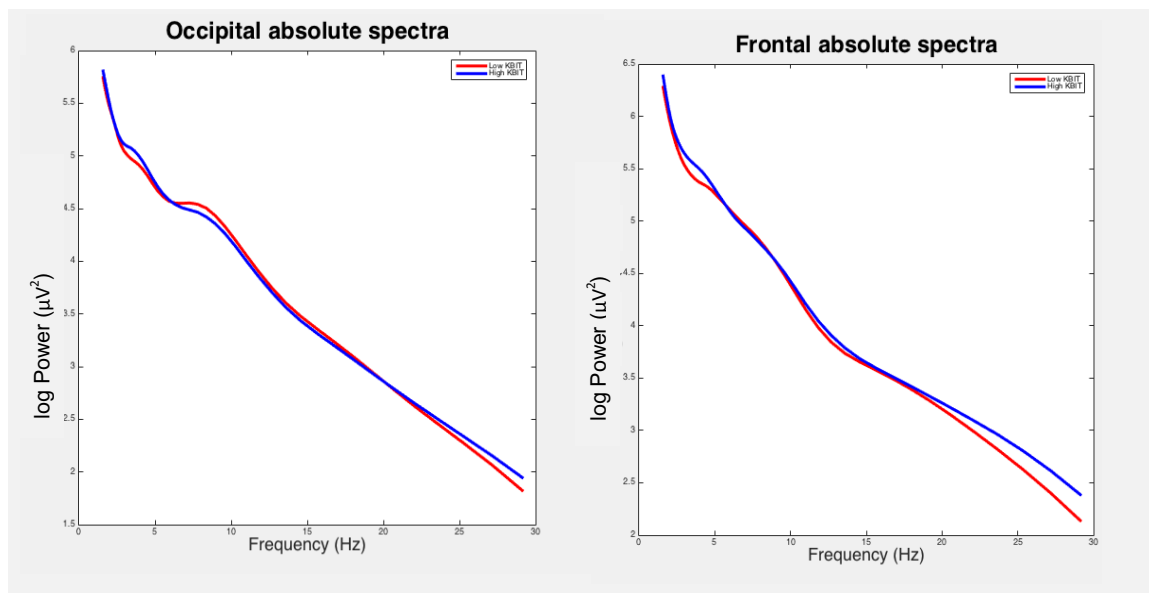


Figure 6.4 EO power-frequency spectrum for median split KBIT-2

Occipital (left) and frontal (right) EO spectra split by raw KBIT-2 score (median split; n=23 per group). High KBIT-2 score shown blue and low KBIT-2 score shown red (2 participants not represented within this chart as their KBIT-2 raw score matched the median value).

6.3.2.4 Adjusted p-value analysis

The above analysis details the results of 36 statistical tests. Due to the exploratory nature of this investigation, p-values have not been adjusted to correct for multiple comparisons. Using a Bonferroni correction (p-values are divided by the number of comparisons; adjusted p-value \leq .001), no EO EEG measures would remain significantly associated with age or general cognitive ability.

6.3.3 Eyes-closed paradigm

6.3.3.1 EC power-frequency and reactivity spectra

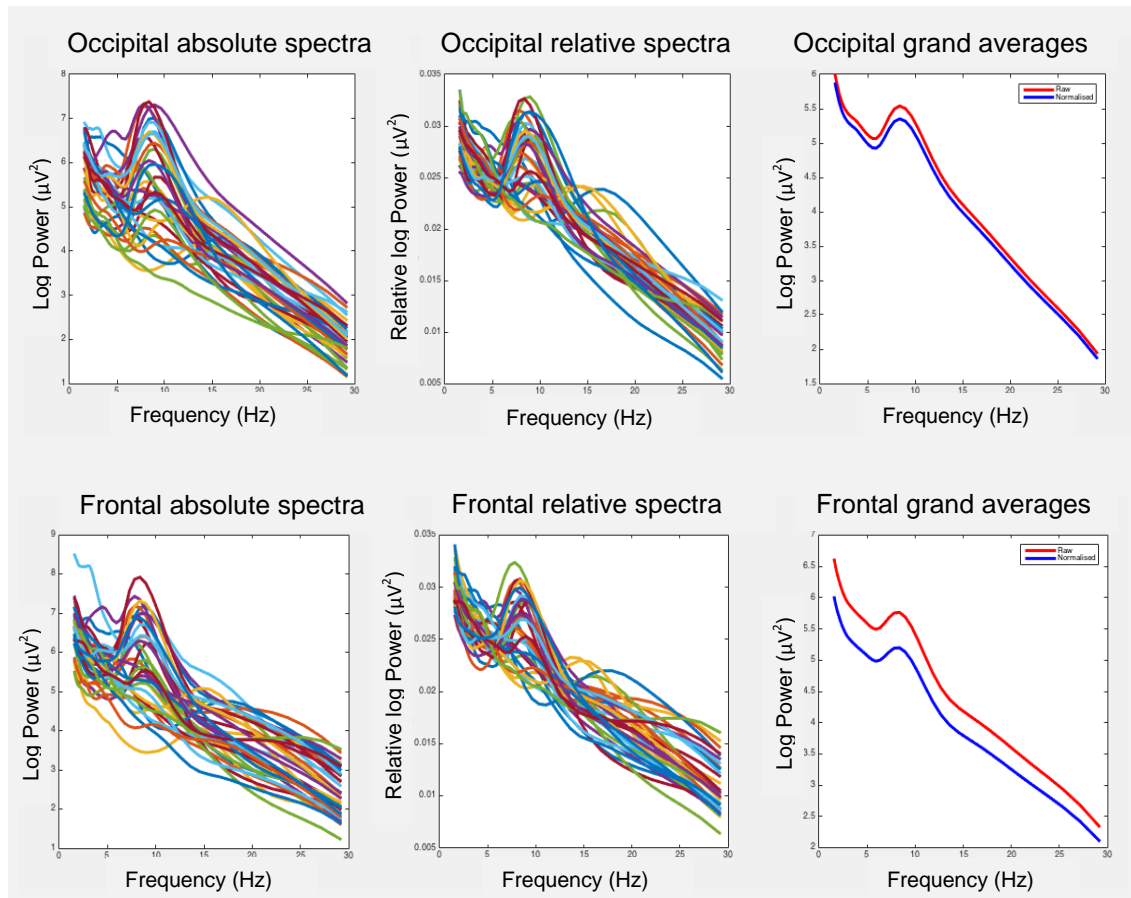


Figure 6.5 EC power-frequency spectra

EC power-frequency spectra for occipital (top) and frontal (bottom) regions. Absolute and relative values are shown for each individual, in addition to absolute (red) and relative (blue) grand averages. Grand average y axis scale corresponds to absolute values (relative value grand average y axis scale not shown).

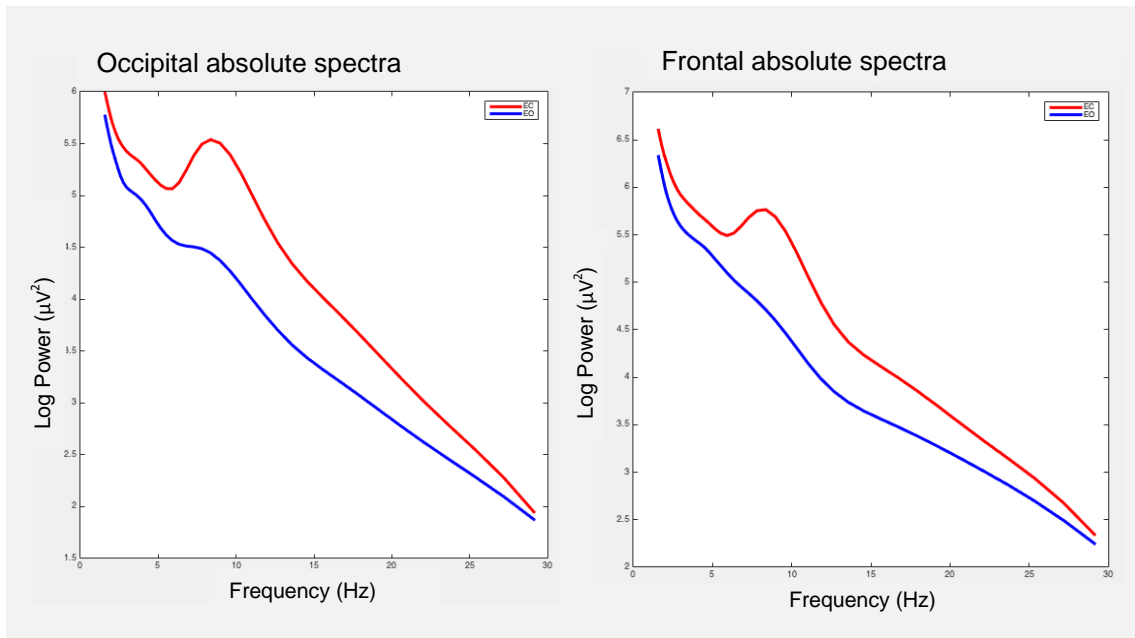


Figure 6.6 Comparison between EO and EC power-frequency spectra

Occipital (left) and frontal (right) EC (red) and EO (blue) EEG spectra. Difference between the two conditions is particularly apparent across the frequency range investigated (4-13 Hz), with peak-suppression in response to eye-opening clearly illustrated by the lack of a peak for the EO condition.

6.3.3.2 EC paradigm: Occipital region results

Using EC data, multiple linear regressions were used to predict EEG measures (stage 1 analysis) for the occipital region (Table 6.4) based on variables of age, paradigm order, and EC paradigm. Multiple linear regressions were then used to predict raw KBIT-2 score based on each EEG measure, in addition to any significant predictors of the relevant measure in stage 1 (stage 2 analysis). In Table 6.4 both stages are shown in individual rows under each EEG measure (green rows). Grey rows show results of multiple regressions with participants aged over 35 removed (n=26 remaining).

EC Occipital: Stage 1 analysis results

For the occipital region (see Table 6.4 and Figure 6.7), age was a significant predictor of EC alpha peak amplitude (increased with increasing age). This relationship did not remain significant when participants over the age of 35 were excluded from analyses.

EC Occipital: Stage 2 analysis results

EC alpha peak amplitude significantly predicted KBIT-2 in this region (raw KBIT-2 score increased with increasing amplitude). The difference in alpha peak amplitude between high and low KBIT-2 scoring participants is illustrated by Figure 6.8. Absolute alpha reactivity ratio was also trending towards significance as a predictor of KBIT-2 in this region (raw KBIT-2 score increased with increasing alpha reactivity). Age was not a significant predictor of KBIT-2 in any regressions for this region.

Eyes-closed; Occipital (n=36)	M (SD)	Equation	Individual predictors	Unstandardised B (SE), Standardised B	Total R ²
Absolute delta power (0.5-4 Hz range) (log μV^2)	5.582 (.565)				
Outcome: Absolute delta power		F(3, 32) = .070, p= .975	Order: p= .712 Paradigm: p= .887 Age: p= .972	.040 (.107), .071; .015 (.102), .026; .000 (.009), .006	.007
Outcome: KBIT-2		F(1, 34) = .689, p= .412	Delta: p= .412	4.903 (5.905), .141	.020
Absolute theta power (4-8 Hz range) (log μV^2)	5.21 (.698)				
Outcome: Absolute theta power		F(3, 32) = 1.043, p= .387	Order: p= .206 Paradigm: p= .555 Age: p= .144	.164 (.127), .237; -.072 (.121), -.105; .017 (.011), .264	.089
Outcome: KBIT-2		F(1, 34) = 2.183, p= .149	Theta: p= .149	6.908 (4.675), .246	.060
Absolute lower-alpha power (8-10 Hz range) (log μV^2)	5.480 (1.097)				
Outcome: Absolute lower-alpha power		F(3, 32) = 1.673, p= .192	Order: p= .197 Paradigm: p= .595 Age: p= .066	.256 (.194), .235; .099 (.185), .092; .032 (.017), .327	.136
Outcome: KBIT-2		F(1, 34) = 1.954, p= .171	Lower-alpha: p= .171	4.175 (2.987), .233	.054
Absolute upper-alpha power (10-13 Hz range) (log μV^2)	4.884 (.785)				
Outcome: Absolute upper-alpha power		F(3, 32) = 1.026, p= .394	Order: p= .365 Paradigm: p= .413 Age: p= .221	.131 (.143), .169; .113 (.136), .146; .016 (.013), .220	.088
Outcome: KBIT-2		F(1, 34) = .680, p= .415	Upper-alpha: p= .415	3.505 (4.250), .140	.020
Absolute beta power (13-30 Hz range) (log μV^2)	3.52 (.545)				
Outcome: Absolute beta power		F(3, 32) = .394, p= .758	Order: p= .444 Paradigm: p= .892 Age: p= .347	.070 (.091), .146; -.012 (.086), -.025; .008 (.008), .173	.036
Outcome: KBIT-2		F(1, 34) = .239, p= .628	Beta: p= .628	-3.390 (6.930), -.084	.007
Absolute peak amplitude (4-13 Hz range; log μV^2)	.504 (.272)				
Outcome: Absolute peak amplitude		F(3, 32) = 3.288, p= .033*	Order: p= .290 Paradigm: p= .218 Age: p= .010**	.049 (.045), .181; .055 (.043), .202; .011 (.004), .442	.236
Outcome: KBIT-2		F(2, 33) = 2.169, p= .130	Peak amp: p= .050* Age: p= .711	25.947 (12.741), .361; -.118 (.315), -.066	.116
Outcome: Absolute peak amplitude	.457 (.268)	F(3, 22) = .829, p= .492	Order: p= .374 Paradigm: p= .690 Age: p= .172	.053 (.059), .197; .023 (.058), .089; .013 (.009), .307	.102
Outcome: KBIT-2		F(1, 24) = 4.299, p= .049*	Peak amp: p= .049*	28.924 (13.951), .390	.152
Absolute peak frequency (4-13 Hz range; log μV^2)	8.075 (2.062)				
Outcome: Absolute peak frequency		F(3, 32) = .776, p= .516	Order: p= .966 Paradigm: p= .292 Age: p= .330	.016 (.379), .008; -.385 (.362), -.189; .033 (.033), .177	.068
Outcome: KBIT-2		F(1, 34) = 1.193, p= .282	Peak freq: p= .282	-1.753 (1.605), -.184	.034
Absolute reactivity ratio (4-13 Hz range; %, minus given 0)	14.111 (7.754)				
Outcome: Absolute reactivity		F(3, 32) = 1.541, p= .223	Order: p= .317 Paradigm: p= .136 Age: p= .566	1.403 (1.381), .182; 2.015 (1.317), .263; .070 (.122), .100	.126

Outcome: KBIT-2		F(1, 34) = 4.060, p= .052	Reactivity: p= .052	.827 (.411), .327	.107
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Table 6.4 EC occipital multiple regression power, alpha peak and alpha reactivity (4-13 Hz) results

Multiple regression results for EEG power, alpha peak and reactivity measures from EC recording condition (n=36) for occipital region. Grey rows show results of multiple regressions with participants aged over 35 removed (n=26 remaining). Asterisk used to denote significance level ($\leq .05^*$, $\leq .01^{**}$, $\leq .001^{***}$). Effect sizes of each model are illustrated with R^2 value. Absolute reactivity ratio values shown are for participants with a negative ratio given zero (if these participants are excluded, all predictors of absolute reactivity ratios remain non-significant. For KBIT-2 outcome, $p = .178$ and total R^2 is .057 for absolute reactivity ratio).

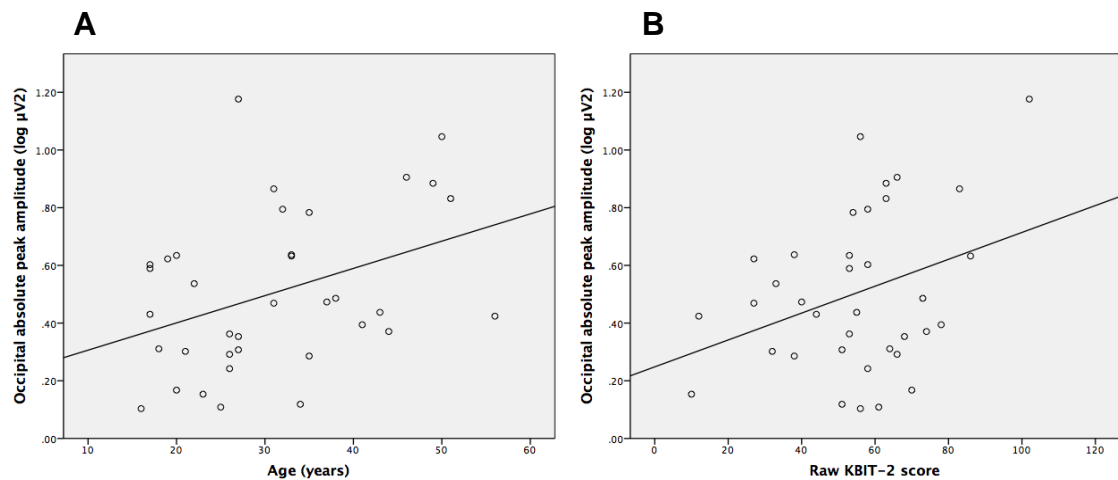


Figure 6.7 Panel of graphs showing significant relationships found for EC Occipital EEG data.

Scatter graphs show the significant positive relationship between age and absolute peak amplitude (A). Scatter graphs also show the significant positive relationship between raw KBIT-2 score and absolute peak amplitude (B). Data is shown for all participants (n=36). Regression lines shown.

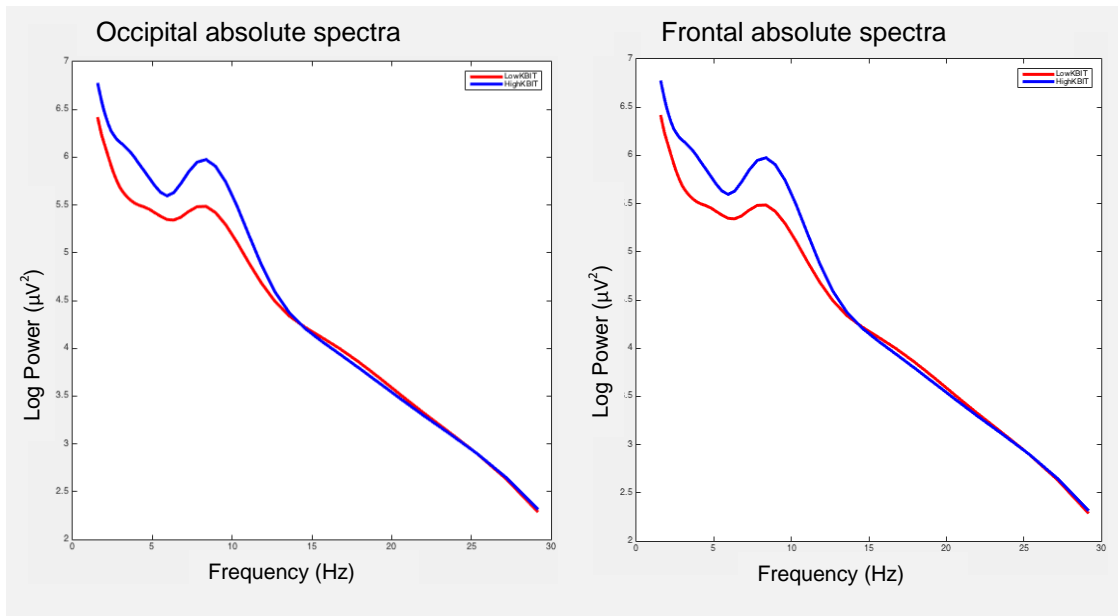


Figure 6.8 EC power-frequency spectrum for median split KBIT-2

Occipital (left) and frontal (right) EC spectra split by raw KBIT-2 score (median split; $n=17$ per group). High KBIT-2 score (blue) and low KBIT-2 score (red) shown (2 participants not represented within this chart as their KBIT-2 raw score matched the median value).

6.3.3.3 EC paradigm: Frontal region results

Using EC data, multiple linear regressions were used to predict EEG measures (stage 1 analysis) for the frontal region (Table 6.5) based on variables of age, paradigm order, and EC paradigm. Multiple linear regressions were then used to predict raw KBIT-2 score based on each EEG measure, in addition to any significant predictors of the relevant measure in stage 1 (stage 2 analysis). In Table 6.5 both stages are shown in individual rows under each EEG measure (green rows). Grey rows show results of multiple regressions with participants aged over 35 removed ($n=26$ remaining).

EC Frontal: Stage 1 analysis results

For the frontal region (see Table 6.5 and Figure 6.9), EC delta power decreased with increasing age. This relationship remained significant, and in fact became stronger, when participants over 35 were excluded. Absolute peak amplitude increased with increasing age, however this was no longer significant when participants over age 35 were excluded.

EC Frontal: Stage 2 analysis results

Theta power and alpha peak amplitude both significantly predicted KBIT-2 score in this region. KBIT-2 significantly increased with higher values on both these EEG measures. The difference in alpha peak amplitude and theta power between high and low KBIT-2 scoring participants is illustrated by Figure 6.8. Lower-alpha power was also trending towards significance as a predictor of KBIT-2 in this region (raw KBIT-2 score increased with increasing lower-alpha power). Age was not a significant predictor of KBIT-2 in any regressions for this region.

Eyes-closed; Frontal (n=36)	M (SD)	Equation	Individual predictors	Unstandardised B (SE), Standardised B	Total R ²
¹ Absolute delta power (0.5-4 Hz range) (log μV^2)	6.060 (.496)				
Outcome: Absolute delta power		F(3, 31) = 2.253, p= .102	Order: p= .173 Paradigm: p= .174 Age: p= .036*	-.121 (.087), -.247; .115 (.082), .234; -.017 (.008), -.375	.179
Outcome: KBIT-2		F(2, 32) = 1.443, P= .251	Delta: p= .105 Age: p= .414	11.791 (7.071), .297; .261 (.315), .147	.083
Outcome: Absolute delta power	6.122 (.441)	F(3, 22) = 3.049, p= .050*	Order: p= .091 Paradigm: p= .189 Age: p= .044*	-.151 (.085), -.339; .115 (.085), .265; -.029 (.014), -.411	.294
Outcome: KBIT-2		F(2, 23) = .744, p= .486	Delta: p= .313 Age: p= .321	10.300 (9.995), .228; .714 (.704), .224	.061
Absolute theta power (4-8 Hz range) (log μV^2)	5.611 (.624)				
Outcome: Absolute theta power		F(3, 32) = .176, p= .912	Order: p= .531 Paradigm: p= .959 Age: p= .656	.075 (.118), .121; .006 (.112), .009; .005 (.010), .082	.016
Outcome: KBIT-2		F(1, 34) = 5.177, p= .029*	Theta: p= .029*	11.448 (5.032), .364	.132
Absolute lower-alpha power (8-10 Hz range) (log μV^2)	5.665 (1.057)				
Outcome: Absolute lower-alpha power		F(3, 32) = 1.046, p= .386	Order: p= .291 Paradigm: p= .476 Age: p= .224	.207 (.192), .197; .132 (.183), .127; .021 (.017), .219	.089
Outcome: KBIT-2		F(1, 34) = 4.011, p= .053	Lower-alpha: p= .053	6.034 (3.013), .325	.106
Absolute upper-alpha power (10-13 Hz range) (log μV^2)	4.933 (.734)				
Outcome: Absolute upper-alpha power		F(3, 32) = .805, p= .500	Order: p= .515 Paradigm: p= .272 Age: p= .541	.089 (.135), .122; .144 (.129), .198; .007 (.012), .110	.070
Outcome: KBIT-2		F(1, 34) = 2.657, p= .112	Upper-alpha: p= .112	7.200 (4.418), .269	.072
Absolute beta power (13-30 Hz range) (log μV^2)	3.520 (.545)				
Outcome: Absolute beta power		F(3, 32) = .758, p= .526	Order: p= .742 Paradigm: p= .391 Age: p= .253	.033 (.100), .062; .083 (.096), .155; .010 (.009), .208	.066
Outcome: KBIT-2		F(1, 34) = .025, p= .874	Beta: p= .874	.985 (6.175), .027	.001
Absolute peak amplitude (4-13 Hz range; log μV^2)	.503 (.292)				
Outcome: Absolute peak amplitude		F(3, 32) = 2.811, p= .055	Order: p= .216 Paradigm: p= .450 Age: p= .012*	.062 (.050), .216; .036 (.047), .125; .012 (.004), .436	.209
Outcome: KBIT-2		F(2, 33) = 2.555, p= .093	Peak amp: p= .034* Age: p= .686	25.984 (11.720), .386; -.127 (.310), -.071	.134
Outcome: Absolute peak amplitude	.462 (.299)	F(3, 22) = 1.682, p= .200	Order: p= .201 Paradigm: p= .747 Age: p= .055	.082 (.062), .272; .020 (.062), .069; .020 (.010), .420	.187
Outcome: KBIT-2		F(1, 24) = 4.466, p= .045*	Peak amp: p= .045*	26.340 (12.464), .396	.157
Absolute peak frequency (4-13	8.105				

Hz range; log μV^2	(2.060)				
Outcome: Absolute peak frequency		F(3, 32) = .667, p= .578	Order: p= .924 Paradigm: p= .333 Age: p= .350	.037 (.381), .018; -.357 (.363), -.176; .032 (.034), .170	.059
Outcome: KBIT-2		F(1, 34) = 1.119 p= .298	Peak freq: p= .298	-1.702 (1.609), -.179	.032

Table 6.5 EC frontal multiple regression power and alpha peak results

Multiple regression results for EEG power and alpha peak measures (4-13 Hz range) from EC recording condition (n=36) for frontal region. Grey rows show results of multiple regressions with participants aged over 35 removed (n=26 remaining). ¹ Denotes an outlier was removed from this EEG measure. Asterisk used to denote significance level ($\leq .05^*$, $\leq .01^{**}$, $\leq .001^{***}$). Effect sizes of each model are illustrated with R^2 value.

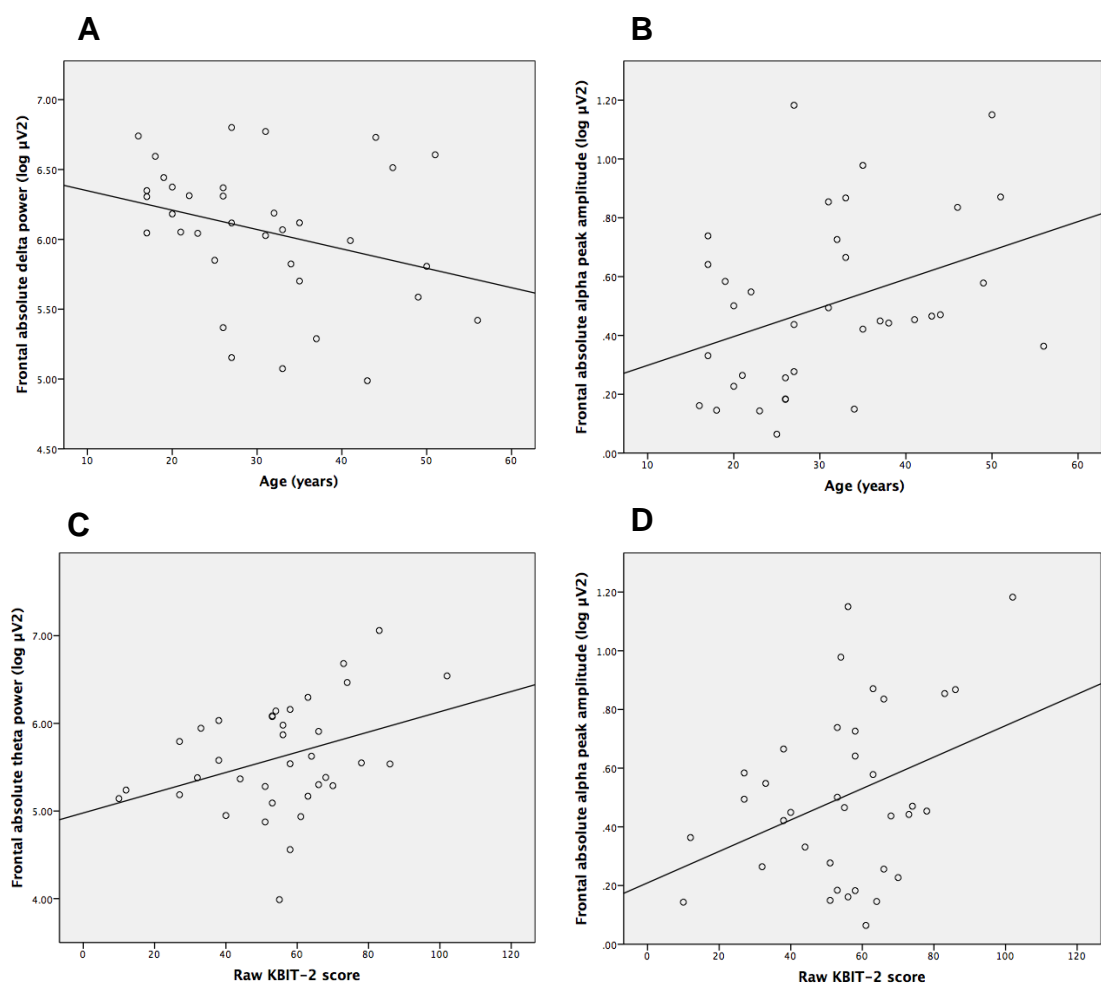


Figure 6.9: Panel of graphs showing significant relationships found for EC Frontal EEG data.

Scatter graphs show the significant negative relationship between age and absolute delta power (A; n=35 due to one outlier removed), and the significant positive relationship between age and absolute alpha peak amplitude (B). Scatter graphs also show the significant positive relationship between raw KBIT-2 score and absolute theta power (C) and absolute alpha peak amplitude (D). Graphs include all participants (n=36) unless otherwise stated.

6.3.3.4 Adjusted p-value analysis

The above analysis details the results of 36 statistical tests. Due to the exploratory nature of this investigation, p-values have not been adjusted to correct for multiple comparisons. Using a Bonferroni correction (p-values are divided by the number of comparisons; adjusted p-value $\leq .001$), no EC EEG measures would remain significantly associated with age or general cognitive ability.

6.3.4 Overall results summary

	EO paradigm		EC paradigm	
	Occipital	Frontal	Occipital	Frontal
Delta power		KBIT-2 (all associations positive)		Age (negative association)
Theta power				KBIT-2 (all associations positive)
Lower-alpha power	Age (positive association)			
Upper-alpha power	Age (positive association)			
Beta power		Age (positive association)		
Peak amplitude	Age (positive association)		KBIT-2 & age (all associations positive)	KBIT-2 & age (all associations positive)
Peak frequency				
EO/EC reactivity	n/a	n/a		n/a






	Age (positive association)
	Age (negative association)
	KBIT-2 (all associations positive)
	KBIT-2 & age (all associations positive)
	Age not significant when >35 yrs excluded

Table 6.6 Summary of results

Summary table illustrating results of this chapter. Significant relationships ($p \leq .05$) between EEG measures and age are shown (positive association dark grey; negative association light grey). Where relationships with age are no longer significant when participants over age 35 are excluded, table segments contain a diagonal black line. Significant relationships between EEG measures and KBIT-2 are shown in blue (all associations positive). EEG measures which have a significant association with both age and KBIT-2 are shown in purple (all associations positive).

6.4 Discussion

6.4.1 Summary of findings

An overall summary of results is provided in section 6.3.4 (above).

6.4.1.1 EO paradigm summary

For the EO paradigm, increasing age was associated with increased alpha power (both lower-alpha and upper-alpha), and increased alpha peak amplitude. These associations were found in the occipital region only. In the frontal region, increasing age was associated with increased beta power. The only EEG measure which remained significantly associated with age when participants over 35 were excluded from analyses was occipital alpha peak amplitude. The relationship between this measure and age became stronger with the exclusion of older participants, and resulted in the strongest effect size found within the EO paradigm ($R^2=.159$).

One EEG measure in the EO paradigm significantly predicted KBIT-2: higher frontal absolute delta power was associated with higher KBIT-2 score.

6.4.1.2 EC paradigm summary

For the EC paradigm, increasing age was associated with decreased delta power in the frontal region, and increased alpha peak amplitude in both regions. Only the association between age and frontal delta power remained significant when participants over age 35 were excluded from analysis. The relationship between this measure and age became stronger with the exclusion of older participants, and resulted in the strongest effect size found within the EC paradigm ($R^2=.294$).

Higher alpha peak amplitude in both regions was associated with higher KBIT-2 score. Higher frontal theta power was also associated with higher KBIT-2 score. In addition to this, higher occipital alpha reactivity and higher frontal lower-alpha power were both trending towards an association with higher KBIT-2 score (trending relationships not shown in Table 6.6).

6.4.1.3 Paradigm comparison

For both paradigms, increasing age was associated with increased alpha peak amplitude. Using values from the occipital region, effect sizes of this relationship were largest for the EC paradigm when all participants were included in analyses ($R^2=.236$ vs $R^2=.097$), and for the EO paradigm when participants over 35 were excluded from analyses ($R^2=.159$ vs $R^2=.102$). Further associations with increasing age and increased

alpha activity (lower-alpha and upper-alpha power) were seen in the EO paradigm alone.

KBIT-2 score was significantly associated with different EEG measures in each paradigm. Age was not significantly associated with general cognitive ability in any analyses for which this variable was accounted for. In EC paradigms, greater frontal theta power and greater alpha peak amplitude in both regions was associated with greater general cognitive ability. In contrast to this, in the EO paradigm greater frontal delta activity was associated with greater general cognitive ability. Effect sizes were largest for the relationship between KBIT-2 and EC measures (occipital peak amplitude, $R^2=.116$; frontal peak amplitude, $R^2=.134$; frontal theta power, $R^2=.132$) compared to EO (frontal absolute delta power, $R^2=.091$).

6.4.2 General cognitive ability

6.4.2.1 Findings in the context of original aims and hypotheses

The primary aim of this chapter was to examine how individual differences in EEG activity are correlated with general cognitive ability in adults with DS (full details of original aims and hypotheses are provided in section 6.1.2). It was hypothesised that lower general cognitive ability would be associated with EC measures indicative of EEG slowing (i.e. slower alpha peak frequency and more power in delta, theta and lower-alpha bands), reduced alpha reactivity, and reduced alpha peak amplitude. No relationships between EEG measures and general cognitive ability were expected for EO data.

As predicted, greater alpha peak amplitude was associated with greater general cognitive ability (greater alpha reactivity was only trending towards this, however). In contrast to original hypotheses, measures indicative of EEG slowing were not associated with lower general cognitive ability. Instead, greater activity in low frequencies (delta and theta; lower-alpha only trending) were associated with greater general cognitive ability. Additionally, there were no significant relationships between alpha peak frequency and cognitive ability. Overall all significant associations between EEG measures and general cognitive ability were found in EC data, apart from one significant relationship was found in EO data only (delta power).

6.4.2.2 Findings in the context of previous research

Peak amplitude itself has not been previously utilised as an EEG measure within DS literature. Alpha band power is commonly used instead. Peak amplitude is, however, a measure that is qualitatively different to band power. It is thought that EEG bands can be explained by an architecture that is centred around peak activity in the alpha (or extended-alpha) range (Babiloni et al., 2010; Klimesch et al., 2004). In this way, the peak of activity in this range is thought of as an anchor-point of the EEG spectrum. It is also noteworthy that the alpha peak is a consequence of neuronal synchronisation (the synchronised activity of similarly oriented neurons firing at a particular frequency, and their activity summing in a measurable peak at the level of the scalp). Desynchronised activity in this band would result in a lower peak or loss of peak, such as that which occurs with eye-opening. Consequently, a higher peak amplitude is indicative of greater neuronal synchronisation in the alpha generating network.

One purported role of alpha activity in cognition is that of an inhibitory attentional filter, with the frequency of the alpha peak acting as a pacemaker for this (Klimesch, 2007; Klimesch, 2011). A further important role associated with the alpha peak is that it is coupled with beta and gamma activity (Carlqvist et al., 2005; Osipova et al., 2008; Bonnefond & Jensen, 2015). Coupling between frequency bands is known to be important in coordinating neural processing (Bonnefond & Jensen, 2015), and coupling deficits have been reported in early stages of AD in the TD population (Poza et al., 2017). Consequently, a lower amplitude of peak activity may negatively impact on these processes and a higher amplitude may be beneficial. In line with this it was demonstrated in the previous chapter that individuals with DS had a lower peak amplitude compared to matched TD controls. The results presented in this chapter therefore appear to show that individuals with a peak amplitude closer to TD-levels (i.e. of higher amplitude) are also closer to TD-levels in regard to general cognitive ability (i.e. higher KBIT-2 score).

Occipital reactivity (or EO/EC ratio) has only been investigated in adults with DS by one previous study. Partanen et al. (1996) found greater reactivity (i.e. larger difference between EC and EO activity) was associated with greater cognitive ability. The same finding was only trending towards significance here. Reactivity is often utilised as a measure of arousal/cerebral activation (e.g. Barry & De Blasio, 2017). It therefore appears that arousal/cerebral activation, as measured by EEG reactivity, may be associated with general cognitive ability in adults with DS; however more research is needed to confirm this. Interestingly studies in the TD population have also shown reactivity to be linked with cognition, by demonstrating reduced reactivity in dementia

and showing this can be used to predict poorer cognitive function at follow-up in those with dementia (van der Hiele et al., 2008).

The findings in this study of increased delta and theta power with greater general cognitive ability is in contrast to most previous studies in DS. For example, Medaglini et al. (1997) reported higher delta and theta power was correlated with lower cognitive ability in adults with DS on a range of tests. However, the present study found associations between delta and cognitive ability only in EO recordings, whereas the delta findings of Medaglini et al. (1997) were from an EC paradigm.

A negative association between theta power and cognitive ability has also been reported by Politoff et al. (1996). This study used 0.4 Hz frequency bins for EEG analysis and reported that power at 4.5 Hz was negatively correlated with cognitive ability. However, the tests of ability used by Politoff et al. (1996) were tests of dementia (MMSE and picture absurdities test). The KBIT-2 used here is instead indicative of IQ score (i.e. general cognitive ability). Consequently direct comparison between these two studies is problematic.

In regard to alpha power, Velikova et al. (2011) reported higher cognitive ability (as measured by a variety of cognitive tests) was associated with higher power at the upper-alpha range and lower power at the lower-alpha range. These findings for lower-alpha are the opposite to those reported here (although the relationship in this study between greater lower-alpha power and greater general cognitive ability was only trending), and no relationships were found here between upper-alpha power and general cognitive ability. However, Velikova et al. (2011) did not exclude individuals with dementia from analyses, which makes comparing these findings to the current study problematic because dementia has been associated with changes in EEG activity (i.e. slowing) in both the DS and TD population.

There are no previous reports of EO resting-state data from adults with DS, aside from a small number of studies which were excluded from the literature review of this thesis due to either testing conditions (EO or EC) being unclear, or if it was unclear whether results referred to EO or EC recordings (outlined in section 2.4.1.3). It is therefore especially problematic to compare the EO findings concerning delta power here with previous DS literature. Interestingly within the TD population delta power, particularly over frontal areas, has been shown to increase with concentration (see Harmony (2015) for a review). As the EO condition here involved participants watching a video –

and was therefore not a classical resting-state task – this could potentially explain why correlations were seen in this paradigm and not in EC data.

As frontal delta is indicative of attention, it would seem logical that participants with greater evidence of attention during EO recordings (i.e. greater frontal delta power) are those with higher general cognitive ability, as found here. A general principle of the functional role of EEG oscillations is that activity in slow frequencies (i.e. delta) are able to travel further distances than faster oscillations, and are therefore posited to be involved in the integration of information between distant brain regions (Moran & Hong, 2011). It is of interest that long-range connections are thought to be particularly impaired in DS (Anderson et al., 2013). Greater frontal delta power may therefore be indicative of less impaired long-range integration, with a measurable impact on general cognitive ability. Connectivity analyses are necessary to explore this further.

6.4.3 Predictors of EEG activity

6.4.3.1 Findings in the context of original aims and hypotheses

Age and paradigm variables

An additional primary aim was to determine whether age or EEG paradigm variables were predictors of any EEG measures (stage 1 analysis). This enabled the influence of these variables to be accounted for when associations between EEG measures and general cognitive ability were investigated (stage 2 analysis). It was hypothesised that measures indicative of slowing (outlined above), in addition to reduced alpha reactivity, would be associated with increasing age in EC measures only (no significant relationships were expected for EO measures and age). Paradigm variables (order and EC paradigm) were not expected to significantly influence any EEG measures.

The influence of age on EEG variables was not in line with these original hypotheses. Instead, increasing age was associated with an increase in power in EO occipital alpha activity (lower-alpha power, upper-alpha power, and alpha peak amplitude), and frontal beta power. In the EC paradigm, increasing age was associated with decreased frontal delta and increased alpha peak amplitude in both regions. As hypothesised, paradigm variables did not significantly influence any EEG measures.

Further exploration of ageing

A secondary aim of this chapter was to investigate whether any relationships with age were still present when older adults (aged over 35) were excluded. This was done in order to exclude individuals who may already have AD neuropathology (but no detectable signs of cognitive decline as measured by the CAMDEX-DS). From this it can be inferred whether significant associations between EEG measures and age are likely to be a consequence of older age (and therefore potentially related to AD neuropathology accumulation), or whether such associations are also significantly present earlier, and therefore may take place across adulthood in individuals with DS.

It was hypothesised that EEG measures predicted by age would remain significant when these individuals were removed from analyses (indicating any ageing effects are more likely to be related to general ageing as opposed to AD neuropathology). Only two measures remained significantly predicted by age when older adults were excluded. These included EO occipital peak amplitude and EC frontal delta power. This finding suggests that these relationships are likely to be linked to maturational or lifespan factors, as opposed to the development of AD neuropathology. Interestingly, effect sizes indicate that both these relationships were strengthened by the exclusion of older participants.

The majority of relationships were no longer significant following the exclusion of older participants (see Table 6.6). Such measures are likely to be mostly influenced by factors affecting older adults with DS (e.g. amyloid accumulation), as opposed to maturational or lifespan changes.

It is of note that relationships between general cognitive ability and EEG measures for which age was a significant predictor in stage 1 analysis (occipital and frontal peak amplitude) remained significant when older adults were excluded from these analyses.

6.4.3.2 Findings in the context of previous research

The lack of age-related slowing of the EEG spectrum (apparent from either power or frequency measures) contrasts with previous research overall. However, it is important to consider that most age-related changes in this study occurred with EO paradigm. Only one previous study in DS that was not excluded from the literature review in this thesis collected EO resting-state data, however this data was only used to obtain EEG reactivity ratios and was not analysed in relation to participant variables. The relationships between EO EEG measures and ageing reported in this study therefore do not contrast with previous findings and instead add to this gap in the literature.

For EC resting-state data, an age-related increase in alpha peak amplitude has not been previously reported, but this EEG measure has also not been utilised by any identified studies. The relationship between alpha peak amplitude and age reported in this study therefore does not contrast with previous findings and instead adds to this gap in the literature. In the TD population, alpha peak amplitude has been shown to increase with increasing age, up to around 20 years of age, before gradually declining during adulthood (Dustman et al., 1999; Marshall et al., 2002; Chiang et al., 2011). Results presented here contrast to what is reported in the TD population and are therefore an interesting finding; particularly as greater peak amplitude was strongly associated with greater general cognitive ability in this population of adults with DS. It may be that protracted maturation of peak amplitude is occurring. Alternatively, the amplitude increase may be compensatory in nature, in response to age-related changes in neurophysiology and/or cognition.

Interestingly, when older adults were excluded from analyses the association between EO occipital absolute alpha peak amplitude and age not only remained significant but also became stronger. In contrast, EC absolute alpha peak amplitude (both frontal and occipital) were no longer significant. This suggests that age-related changes in EC alpha peak amplitude may be more associated with old age (defined as over age 35 for the purpose of this study), as opposed to lifespan changes. This would therefore fit more with the hypothesis that changes in this measure are a compensatory response to ageing and/or development of AD pathology, as opposed to a change linked to delayed maturation. In contrast, EO alpha peak amplitude may be a measure that is more associated with delayed maturation than ageing.

In this study EC frontal delta power decreased with increasing age. Specific associations between age and delta power in adults with DS have not been previously reported – instead overall “slowing” of the EEG spectrum is attributed to an increase in theta power and a decrease in power of faster bands. It is unclear why the current study found an association between delta and age that has not been identified by previous studies. In the TD population there is also lack of consensus regarding the effect of age on delta power (Babiloni et al., 2006; Vlahou et al., 2014; Rossini et al., 2007). In the present study when older adults were excluded from analyses, the relationship between frontal delta power and age remained significant. This suggests EC and frontal delta power may decrease across adulthood.

In contrast to findings here, one study has reported an age-related decrease in upper-alpha and beta power in DS (Murata et al., 1994), whereas in the present study these measures increased with age. Reasons for the contrasting findings between the current study and Murata et al. (1994) are unclear, however individuals with cognitive decline or dementia were not excluded by Murata et al. (1994), which could therefore have confounded these results. It is of note that in the TD population, beta power is thought to increase with age (Babiloni et al., 2006; Rossini et al., 2007; Vlahou et al., 2014), as found in the current study. Associations between age and upper-alpha and beta power did not remain significant when older participants were excluded, indicating age-related changes in these measures are likely to be associated with older age in this population.

No associations between age and alpha peak frequency were identified in this study, which is in contrast to previous research (see section 2.4.2.2). It is possible that the lack of findings in the present study regarding this measure are a consequence of excluding individuals with cognitive decline or a diagnosis of dementia. When considering only previous studies which have attempted to control for the potentially confounding presence of cognitive decline on this measure, Locatelli et al. (1996) did not find a significant relationship between alpha peak frequency and age, however Murata et al. (1994) and Katada et al. (2000) both reported a decrease in alpha peak frequency with increasing age.

6.4.4 Regional differences

6.4.4.1 Findings in the context of original aims and hypotheses

A further secondary aim of this chapter was to investigate whether findings differed between occipital and frontal regions. It was hypothesised that significant relationships with delta and theta activity would be found in frontal regions only, whereas relationships with alpha activity would be in occipital regions only. No differences between regions were expected for any relationships with beta activity.

In line with these hypotheses, associations of general cognitive ability with both delta and theta power were found in the frontal region only. However, associations between general cognitive ability and alpha peak amplitude were found in both regions.

In line with hypotheses, delta power was only significantly associated with age in the frontal region, and alpha power associations with age were found only in the occipital

region (however alpha peak amplitude was significantly associated with age in both regions). The association between beta power and age was found only in the frontal region, which was not hypothesised.

6.4.4.2 Findings in the context of previous research

It seems reasonable to assume that relationships between EEG activity and general cognitive ability are more likely to be identified where activity within each band is strongest. It is therefore likely the regional pattern of findings reported here are due to delta and theta activity being stronger in frontal regions compared to occipital, and alpha activity being strongest over the occipital region compared to frontal (apparent from mean power values over each region). This distribution of power is as would be expected based on knowledge of EEG activity in the TD population. In line with this, within the DS literature associations between cognitive ability and alpha power are reported for occipital regions (Soininen et al., 1993; Locatelli et al., 1996; Politoff et al., 1996; Medaglini et al., 1997; Velikova et al., 2011). However, associations between cognitive ability and delta and theta power have been reported across the scalp (Politoff et al., 1996; Medaglini et al., 1997; Velikova et al., 2011). Potential issues comparing these three studies to the present study are discussed in section 6.4.2.2.

6.4.6 Strengths, limitations and future research

This chapter details the analysis of resting-state EEG data collected from 48 adults with DS, which is a relatively large study of this type. The study is also in-depth, with both EO and EC data analysed (in addition to differences between these spectrums explored), and activity from two distinct regions (occipital and frontal) examined. The study also benefits from genetic testing to ensure all participants have trisomy 21, and the use of cognitive and medical screening to ensure only participants without cognitive decline and without a diagnosis of dementia are included in analyses. This has allowed a comprehensive and valid assessment of the relationship between EEG characteristics and general cognitive ability (pre-decline) in adults with DS.

The study is limited by lack of gamma band investigation, as in the previous chapter (discussed in section 5.4.3). Gamma band frequencies may be particularly useful to look at in the future as this would enable alpha-gamma coupling to be examined. As previously discussed, alpha-gamma coupling is thought to be important in cognition. Differences in coupling between adults with DS may therefore contribute to differences in general cognitive ability. Furthermore, examining alpha-gamma coupling would help

to interpret whether these processes are related to peak amplitude, and whether this is the mechanism through which peak amplitude is associated with general cognitive ability in adults with DS. Future studies would therefore benefit from including gamma band frequencies in analysis. As discussed previously, gamma was not examined in the current study due to the high prevalence of muscle artifacts and electrical noise within this region of the EEG spectrum.

Similarly to the previous chapter, although the oldest participant in this sample was 56, the mean age of this sample is relatively young (30.9 and 30.0 for EC and EO paradigms respectively), and so results cannot easily be generalised to older adults with DS. As ageing effects have been identified, further studies of individuals with dementia or cognitive decline, and longitudinal studies and/or studies targeted at particular age groups would be beneficial to further elucidate these relationships.

A limitation specific to this chapter is the use of KBIT-2 score as a single measure of general cognitive ability. Assessment of general cognitive ability in those with DS is problematic due to many existing neuropsychological tests producing floor-effects, especially when standardised scores are used (d'Ardhuy et al., 2015; Sinai et al., 2016; Glenn & Cunningham, 2005). As discussed in section 1.3.3, a variety of IQ tests have been used in studies assessing general cognitive ability in adults with DS, however raw KBIT-2 score has been used by more recent studies as raw KBIT-2 scores benefit from minimal floor-effects (de Sola et al., 2015; Edgin et al., 2010; Sinai et al., 2016; Startin et al., 2016). The use of raw KBIT-2 scores is therefore a strength of this study (enabling individuals with even severe ID to be assessed and included), however the study may have benefitted from the inclusion of an additional measure of general ability (e.g. an adaptive behaviour measure). However, I have chosen not to include other measures to reduce the chance of a type 1 statistical error (similarly to why additional brain regions and relative power values were not analysed).

Due to the in-depth exploration of EEG data in this chapter, many statistical tests have been used and p-values have not been adjusted to compensate for this. There is therefore the possibility of a type 1 statistical error. Using more stringent criteria (i.e. $p \leq .01$) may improve the validity of findings, however due to the exploratory nature of this study this was not implemented and therefore remains a potential limitation of this analysis.

A further potential limitation of analysis is that the approach taken of excluding adults over 35 to explore any ageing effects further. It was assumed that significant

relationships between EEG measures and age that did not withstand the exclusion of older adults indicated effects had been driven by these older adults, and therefore age effects were related to older age (and by implication the development of AD pathology in DS) and not a consequence of general ageing across adulthood. However, excluding these individuals also reduced sample size (13 and 10 participants excluded for EO and EC paradigms respectively), which in turn reduced statistical power. The loss of significant age-related changes in EEG measures with the exclusion of older adults may therefore potentially be confounded by this.

It appears that the sample sizes of these paradigms were adequate to detect significant associations between EEG variables and cognitive and participant variables. However, lack of statistical sensitivity could be contributing to the failure in some cases to replicate previous findings (e.g. associations with alpha peak frequency). This may be particularly true in the EC paradigm, which had a smaller sample size compared to EO. It is therefore likely that larger studies would be beneficial.

An additional potential limitation of this study to consider is that cognitive assessment was carried out in a separate session to EEG data acquisition. The median time delay between assessments was around 2.3 months for adults aged 36 years and above and 3 months for adults aged 16-35 years (see section 3.1). There was also a large range in time between sessions that should be considered (max 265 days for older adults; max 761 days for younger adults). It is unlikely KBIT-2 performance would have changed within this period of time for younger adults, as cognitive decline is not expected, however for older adults this is possible. Consequently, some older individuals included in this study may have been experiencing early signs of decline that had not been identified. It is worthwhile noting that this is always a limitation to consider in any study attempting to exclude individuals with cognitive decline, as it is difficult to accurately measure.

Extending sessions to include cognitive testing at the same time as recording EEGs would have had its own limitations in terms of participant attention and compliance. This is because both cognitive assessment and EEG acquisition can be time consuming in this population due to additional protocols for consent and extra time necessary to explain instructions, for example. Despite this, future research would benefit from ensuring cognitive testing is as close to the EEG session as possible.

Finally, EO resting-state data was collected while participants viewed a silent cartoon. Such an approach is common in paediatric populations and also common in studies

involving adults with an ID (e.g. Wang et al., 2017). In contrast, classical EO resting-state paradigms collected from TD adults involve participants viewing a fixation cross on a screen. It is therefore likely the paradigm implemented here resulted in additional visual cortex stimulation (e.g. motion detection and processing) compared to such classical paradigms. A level of caution should therefore be taken in comparing the EO results in this thesis to EO resting-state studies where a fixation cross has been used. This is also true of reactivity measures, which may have been impacted by visual stimulation in EO recordings.

6.4.7 Conclusions

In this study, differing relationships between EEG measures and variables of interest were found for each paradigm. It appears that EO resting-state EEG measures may be more useful for examining age-related change in DS, whereas EC resting-state EEG measures may be more sensitive to individual differences in general cognitive ability.

Overall, age-related slowing of the EEG spectrum did not occur and age was not associated with general cognitive ability in any analyses. Instead increasing age was associated with an increase in alpha and beta activity in the EO paradigm. Increasing age was associated with an increase in alpha peak amplitude in the EC paradigm, in addition to a decrease in delta activity in this paradigm.

In EO data, greater frontal delta power is related to greater general cognitive ability; potentially through mechanisms related to improved attentional engagement. In EC data, it appears that theta-alpha oscillations are associated with general cognitive ability, with greater general cognitive ability related to higher peak amplitude in both regions and higher theta power in frontal regions (also trending but not significant were associations between greater general cognitive ability with greater occipital alpha reactivity, and greater general cognitive ability with greater frontal lower-alpha power). Due to these findings and also previous studies highlighting these oscillations as important, further investigation of the theta-alpha network in DS is warranted.

The following chapter will explore this network using dynamic causal modelling. This technique allows potential neurophysiological mechanisms underlying individual differences in theta-alpha activity and associations between this and general cognitive ability to be elucidated.

Chapter 7 Dynamic causal modelling of EEG activity

7.1 Introduction

The previous chapter demonstrated the relationship between theta-alpha oscillations and KBIT-2 performance in adults with DS. This chapter aims to model this relationship using dynamic causal modelling (DCM). DCM allows connectivity parameters between specified brain regions to be estimated, and from this the role of potential underlying neurophysiological connections within and between cell populations to be elucidated (for example, the balance between excitatory and inhibitory connections).

Understanding the relationship between these neurophysiological connections and general cognitive ability in adults with DS is important for informing biomarker and drug target search. This is also a particularly pertinent area of research as work from animal models suggests that imbalances in excitatory/inhibitory (E/I) mechanisms contribute to cognitive impairment in DS (see section 7.1.2). Investigating how E/I mechanisms may mediate the relationship between general cognitive ability and theta-alpha activity is therefore important. Further, to date no previous studies have reported modelling of brain activity in people with DS or other forms of ID, indicating the importance of conducting such analysis.

7.1.1 Dynamic Causal Modelling

Modelling brain activity follows similar steps to any form of scientific modelling. By definition “modelling” is simply a method for representing or approximating data. At a basic level, for instance, the mathematical mean is a model that is commonly used to represent (or “model”) an entire dataset. Dynamic models can be used to provide information over time and are therefore particularly suited to brain imaging data. As a consequence of providing information over time, dynamic models are also able to provide information on the direction of relationships (i.e. causal relationships). For this reason, DCM is often used to provide measures of directed connectivity (also known as “effective connectivity”) with brain imaging data. Originally developed for fMRI by Friston et al. (2003), DCM for EEG has become increasingly popular and there is now a large literature on these methods, including DCM for resting-state activity (known as DCM for steady-state responses) (e.g. Moran et al., 2007, 2008, 2009, 2011).

In essence DCM involves the creation of a “synthetic brain” (the model), which is able to simulate the generation of EEG data over pre-defined regions and frequencies of interest. In this instance, regions of interest are nodes across the alpha network and frequencies of interest are 4-13 Hz (informed by previous literature and findings within this thesis). The simulated EEG data generated by this synthetic brain is then compared to real data collected from participants. Neurophysiological properties of the synthetic brain (encoded by a multitude of differential equations representing the activity of different neuronal populations) are adjusted to obtain an optimal fit between synthetic and participant EEG data. Different hypotheses can then be tested as to which aspects of the model are the most important parameters influencing relationships of interest (in this case, which model parameters are correlated with raw KBIT-2 score and age). Examples of model parameters which may be important include E/I forward or backward connections between network nodes, or E/I intrinsic connections within network nodes. Within network nodes, E/I parameters can be an overall E/I measure of that node or refer to individual E/I contributors (e.g. E/I connections between two specific cell populations). Competing hypotheses are evaluated based on their model evidence; a process known as Bayesian model selection.

Although still a relatively new technique, DCM studies within clinical populations have produced evidence regarding aberrant effective connectivity patterns in depression (Li et al., 2017), schizophrenia (Zheng et al., 2017), psychosis (Díez et al., 2017), Tourette syndrome (Zapparoli et al., 2017) and addiction (Zare Sadeghi et al., 2017). A particular strength of DCM is that it extends beyond traditional methods of connectivity analyses, which simply describe differences in data, to offer mechanistic insights into the underlying causes of such differences (e.g. functional connectivity measures describe non-directional statistical dependencies between brain regions but lack a causal description). DCM methods also allow inferences about neuronal states that are not directly measurable themselves to be made (Vanvinckenroye et al., 2016), for instance the E/I micro-circuitry mediating neuronal activity. It is for this reason DCM has been referred to as a “mathematical microscope” (Moran et al., 2011).

7.1.2 Excitation/Inhibition balance in DS

A range of different mouse models have been developed that contain extra copies of genes that are similar to the extra chromosome 21 genes found in humans with DS. These mouse models of DS also display phenotypic features comparable to those found in humans with DS, including deficits in learning and memory. Cognition in mouse models of DS is measured through a range of behavioural tests. For example

the Morris water maze, which involves mice learning to locate a submerged platform using environmental cues. E/I in mouse models can be measured through a variety of techniques, including electrophysiological recordings (both in vivo and in vitro) and analysis of neural tissue post-mortem. Crucially, mouse model studies (using the Ts65Dn mouse model; see section 7.4.2 below for further details) have indicated that cognitive impairment in DS may be largely due to a shift in E/I balance to a state of over-inhibition (Fernandez et al., 2007; Braudeau et al., 2011; Contestabile et al., 2017).

In contrast, results from a range of human methodologies (including the analysis of neural tissue post-mortem and in vivo measurement of neurotransmitter levels using magnetic resonance spectroscopy (MRS)) have indicated that GABAergic inhibition may in fact be reduced in individuals with DS relative to TD controls (Whittle et al., 2007; Reynolds & Warner, 1988; Smigielska-Kuzia et al., 2010; Bhattacharyya et al., 2009; Ross et al., 1984). Moreover a recent human drug trial aimed at improving cognitive function in DS by targeting the hypothesis of increased cortical inhibition was unsuccessful using a GABA inverse agonist, with the trial finding no significant difference in cognitive ability after 26 weeks (Roche, 2016). The contradictory findings between human and animal work in this field, and important ramifications in terms of unsuccessful clinical trials, highlight the need to elucidate the role of E/I balance in DS.

7.1.3 Aim and hypotheses

The primary aim of this chapter was to use DCM for steady-state responses to examine potential neurophysiological mechanisms underlying the relationship between EC resting-state 4-13 Hz activity and raw KBIT-2 score in adults with DS, by modelling the alpha-generating network.

Based on animal model studies it was hypothesised that inhibition would be the most important network parameter associated with KBIT-2 performance. Specifically, there would be an inverse relationship between inhibition and KBIT-2 score, with lower inhibition associated with higher KBIT-2 score.

A secondary aim of this analysis was to explore effects of age on parameters of this model. Based on findings in the previous chapter, it was hypothesised age would exert effects on these parameters in the same direction as KBIT-2, with lower inhibition associated with increasing age. Individuals over 35 were not excluded from these analyses as a wide age range is suited to the exploratory aims of this chapter.

7.2 Methods

7.2.1 Participants

As correlations between theta-alpha activity and KBIT-2 score were found within the EC paradigm in Chapter 6, this group of participants was used for DCM analysis presented here. This included 36 adults with DS (17M:19F) of mean age 30.92 years (11.03 SD), ranging from 16 to 56 years. Raw KBIT-2 score ($M = 54.83$ (19.64 SD)) ranged from 10 to 102, as in the previous chapter. All participants had genetically confirmed trisomy 21 and no participants had a clinical diagnosis of dementia or evidence of cognitive decline according to the CAMDEX-DS.

The following is an explicit list of inclusion criteria for participants in this chapter:

- Sufficient data EC resting-state data (≥ 12 2-second segments) was obtained from the participant during the EEG testing session
- Participant has genetically confirmed trisomy 21
- Participant did not show evidence of cognitive decline or have a diagnosis of dementia at the time of cognitive assessment

7.2.2 EEG procedures

EEG acquisition and pre-processing was identical to those used previously (see methods sections 3.7.1 & 3.7.2, and Chapter 5 section 5.2.3 for full details). Analysis of the EEG signal deviated, however, in that power-frequency spectral estimates were obtained using multitaper analysis (performed on non-overlapping 2-second epochs (≥ 12) for every channel), as opposed to wavelet analysis. Additionally, only the absolute EEG signal was used within this chapter. Multitaper analysis (Thompson, 1982) is an alternative Fourier analysis method for signal decomposition, and has similar benefits to wavelet methods in terms of overcoming limitations of traditional Fourier methods (discussed in section “3.7.2 EEG measures”). The reason for this differing decomposition method is that multitaper analysis is the method implemented within the Statistical Parametric Mapping (SPM) toolbox (Eickhoff et al., 2005), and is commonly used in DCM for steady-state responses (e.g. Pinotsis et al., 2012). Power-frequency spectral estimates from these two methods should not differ, but the multitaper method implemented here is thought to benefit from greater frequency specificity (van Vugt et

al., 2007). Within this chapter all analysis was performed with MATLAB software (version R2014b) installed with the latest version of the open source SPM toolbox (version 12), in addition to customised MATLAB scripts.

7.2.3 DCM procedures

Results from the Chapter 6 act as an intermediate step for this analysis by providing prior information about potential regions and frequencies of interest for DCM analysis. DCM is a hypothesis driven method that requires such prior information. Associations between cognitive ability and both occipital and frontal activity in the theta-alpha range (power and peak amplitude measures), were demonstrated in Chapter 6. This provides prior evidence for involvement of the network generating these frequencies across the scalp (opposed to within a discrete region). It is important to note here that alpha oscillations are known to operate across a wider frequency range than 8-13 Hz (Haegens et al., 2014). For many individuals, significant portions of alpha activity fall outside this fixed frequency window. This is likely to be particularly true in adults with DS, where in Chapter 6 individual peak frequency values were demonstrated as falling across the 4-13 Hz range, and because of evidence suggesting that alpha oscillations are centred around peak values (Klimesch et al., 2004). Consequently it may be more accurate to consider modelling the 4-13 Hz frequencies of interest here as modelling the extended alpha range. For this reason, network nodes of interest were chosen based on alpha network literature.

In DCM, nodes of interest are always chosen a priori based on previous literature. Based on studies analysing EEG activity in combination with fMRI or TMS (Laufs et al., 2003; Omata et al., 2013; Bonnard et al., 2016; Li et al., 2017; Dai et al., 2017), bilateral nodes of interest in the alpha network were chosen in occipital, parietal, and frontal regions. These were specified to be located in the primary visual cortex (V1), superior parietal lobule (SPL), and middle frontal gyrus (MFG) respectively. Selection of these nodes enabled investigation of a distributed bilateral network across the cortex (see Figure 7.1).

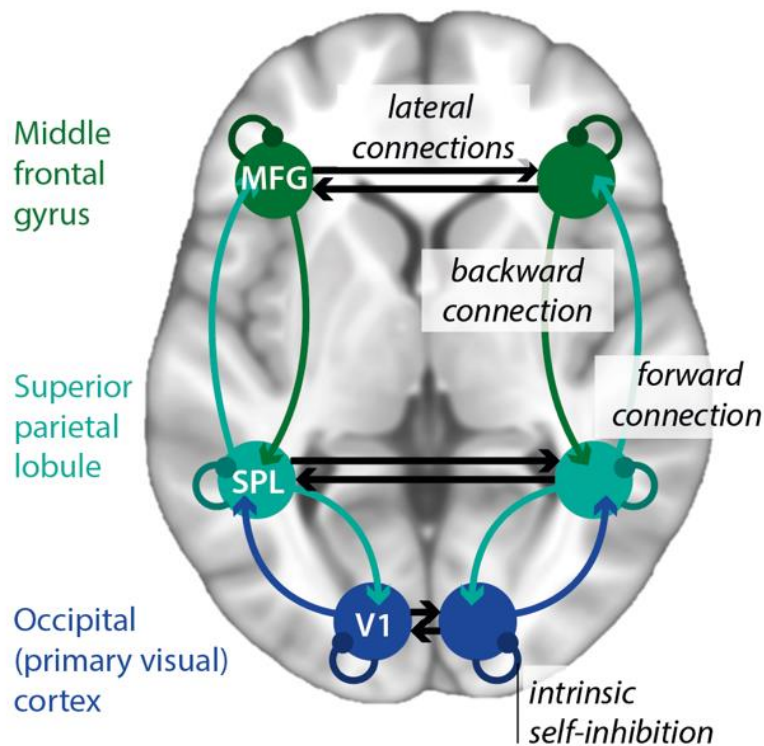


Figure 7.1 Network nodes

Illustration of the predefined distributed bilateral network investigated with DCM. Nodes of interest include primary visual cortex (blue), superior parietal lobule (teal) and middle frontal gyrus (green). Lateral connections between bilateral nodes are shown (black). Also shown for each node are forward and backward connections, and intrinsic self-inhibitory connections for each node.

Within each node, a canonical microcircuit (CMC) neural mass model (Bastos et al., 2012) was implemented (see Figure 7.2). The CMC simulates the electrophysiological activity of each node within the chosen network using mathematic equations to represent biologically plausible cellular activity. For example, differential equations are used to describe the postsynaptic activity of a cell population based on its presynaptic input. The CMC represents the activity of specific cell populations and their connections. Cell populations represented within the CMC implemented here include superficial pyramidal cells, deep pyramidal cells, spiny stellate cells, and inhibitory interneurons (Bastos et al., 2012). Connections represented include E/I extrinsic, intrinsic, and self-connections for each cell population. Connections follow standard anatomical rules (e.g. forward connections target spiny stellate cells; backward connections target pyramidal cells). The CMC is combined with a second model (the observation model) which accounts for the propagation of signals through head tissues (Vanvinckenroye et al., 2016). These models together were used to generate synthetic EEG data at the predefined nodes of interest (Figure 7.1).

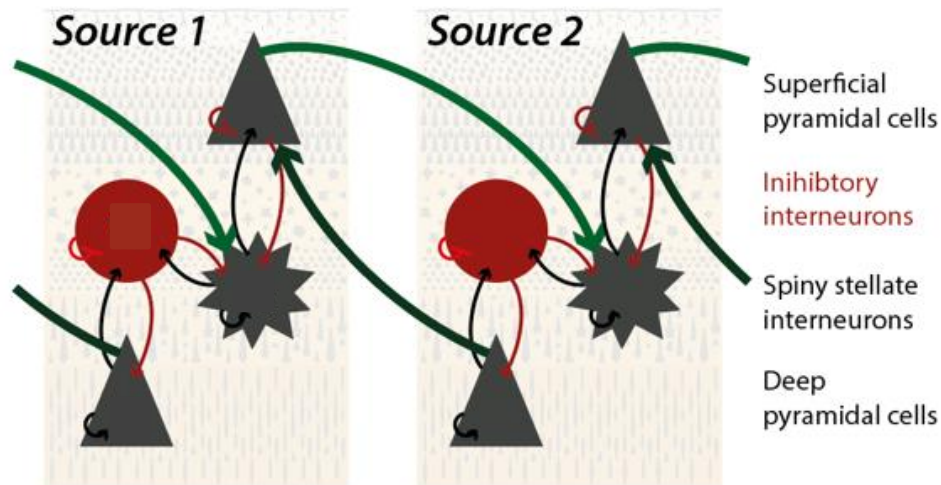


Figure 7.2 Microcircuit model within each node

Illustration of the CMC neural mass model within each node of interest. Two nodes are shown (source 1 and source 2). Superficial pyramidal cells (triangle), deep pyramidal cells (triangle), spiny stellate cells (spiky circle), and inhibitory interneurons (circle) are represented. Also represented are within-population self-connections, between-population connections, and between-node connections.

This standard CMC was optimised to generate alpha oscillations through a process known as tuning of priors. Here priors refer to physiological assumptions about synaptic parameters (e.g. time constants representing the kinetics of different synapses). Standard priors within the CMC are optimised for modelling event-related potentials, as these were the first form of EEG data analysed with DCM techniques and are still commonly analysed today. It is therefore necessary for researchers investigating resting-state activity to tune these standard priors towards their effects of interest (in this case 4-13 Hz activity).

The priors were tuned by a two-step approach. Firstly, several time constants (parameters T1, 2, 3) were increased and population variance (parameter S) was decreased. These adjustments were made based on spectral predictions of individual parameters on the spectral output of the CMC (spectral predictions themselves were based on tools within the SPM environment that show the effect of altering individual parameters on spectral output). The effects of this tuning on spectral output was then assessed for all subjects through the process of “model inversion”, during which data is generated by the model and optimised to fit each individual’s recorded scalp data through an iterative loop. The resulting fit between generated and recorded data was

then compared for each subject. It was determined that good model fits were only achieved for a small number of subjects. As a second step, the parameters from one inversion that achieved a good model fit were selected and used as priors to further tune the model priors for a second round of model inversions. This second round of model inversions achieved good fits for all participants (see Figure 7.5). It is the results of these inversions that are reported in this chapter.

Model inversion – the process by which synthetic data is generated by the model and optimised to fit recorded scalp data – is here achieved by a method known as DCM for cross-spectral densities (CSD). In this method, data is represented in the frequency domain (as opposed to the time domain used in DCM for ERPs), and so this method is used for EEG resting-state data (Kiebel et al., 2009; Moran et al., 2009). The CSD is a simple but comprehensive summary of neuronal activity from multiple sources across the frequency spectrum.

CSDs can be visualised by summarising the data they contain in terms of their principal eigenmodes (representing the main components of the data). Here, CSDs (both model-generated and whole-scalp) were decomposed into eight principal eigenmodes, and the highest three were visualised for each participant (see Figure 7.4). It is CSD eigenmodes that are used to fit model-generated data to whole-scalp data during the process of model inversion. The fit of CSD eigenmodes is achieved by changing the weight of model parameters (i.e. synaptic parameters of intrinsic and extrinsic connections in the network). It is these changes in the weight of model parameters that allow inferences about underlying network differences between participants to be made.

Inferences about underlying network differences between participants, based on changes made in model parameters during model inversion, are determined with Bayesian inference. The process of identifying which changes in model parameters best explain the data (in this case the observed differences in 4-13 Hz activity in relation to KBIT-2 score and age) is achieved through Bayesian Model Reduction and Bayesian Model Selection (Penny et al., 2004; Friston et al., 2015). This method uses Bayesian statistics to test the association between raw KBIT-2 score and age with connectivity parameters of pre-defined network-level candidate models (Figure 7.3). For each model, Bayes' rule is used to determine the probability of the model parameters, given the observed data and the model. This probability provides a measure of model evidence, which is used as the basis to compare competing candidate models. Seven candidate models were tested here, differing in terms of

forward, backward, and intrinsic self-inhibitory connections (Figure 7.4). Both raw KBIT-2 score and age, and their interaction effect, were used as factors in the model. In addition, two noise regressors were also included (counterbalanced order and whether the EC paradigm was split or whole block). Any effects of these experimental variables were therefore accounted for within the model.

The model with the greatest log-evidence (a free energy approximation) was selected as the “winning model” (i.e. the best model) of all seven candidate models tested. Log-evidence is a measure of “model goodness”, which is a trade-off between model accuracy and model complexity (Mackay, 2003). In DCM, a good model explains the data as accurately as possible with minimal complexity. The winning network-level model was then examined to identify parameter changes associated with KBIT-2 score and age at each individual node of the network.

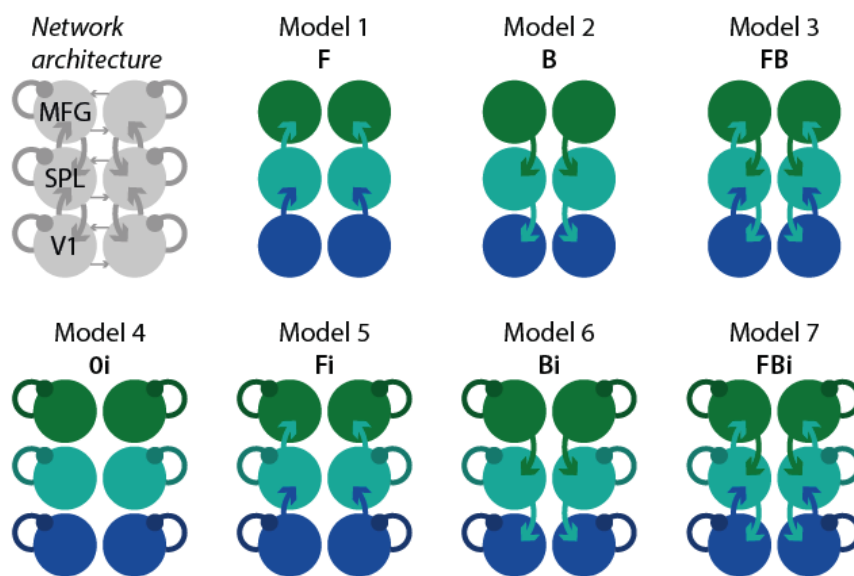


Figure 7.3 Candidate models

Seven candidate network-level models tested during Bayesian Model Selection to identify which changes in network-level model parameters (i.e. directed connectivity) best explain the observed differences in 4-13 Hz power in relation to KBIT-2 score and age between individuals with DS. Models differed in terms of allowing variables (KBIT-2 score and age) to exert effects on only forward connections (F), only backward connections (B), forward and backward connections (FB), only intrinsic self-inhibition (Oi), intrinsic self-inhibition and forward connections (Fi), intrinsic self-inhibition and backward connections (Bi), and intrinsic self-inhibition in addition to both forward and backward connections (FBi).

7.3 Results

A bilateral alpha network containing nodes within V1, SPL and MFG was first created (Figure 7.1). Each node contained a CMC neural mass model (Figure 7.2), which was tuned to generate alpha oscillations. Data generated by this model was compared to data recorded from 36 individual participants with genetically confirmed trisomy 21 (17M:19F; mean age 30.92 years (11.03 SD); 16-56 year range) and no evidence of noticeable cognitive decline. Specifically, for each participant, model-generated data and whole-scalp data were decomposed into CSDs represented by eight principal eigenmodes, and fit was optimised through the process of model inversion. The power of the top three eigenmodes across the 1-30 Hz frequency spectrum were plotted in order to visually compare model-generated data and whole-scalp data (Figure 7.4). These were used to assess how successfully the model was capturing activity of interest (4-13 Hz range) at the level of each individual. It was concluded the model was successfully capturing this activity.

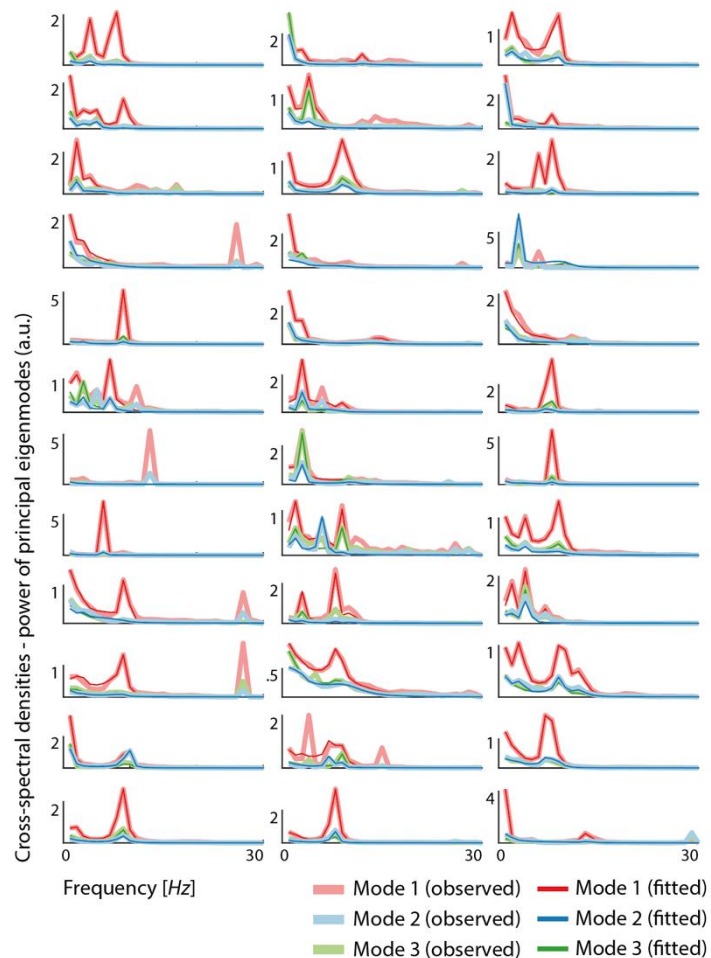


Figure 7.4 Individual subject model fits

Diagram illustrating individual subject model fits ($n=36$). The top three eigenmodes (red, blue and green respectively) obtained from CSDs of model-generated (thin bright line) and whole-scalp (thick pale line) are shown for each participant.

Seven pre-defined network-level candidate models (Figure 7.3) were then compared. This was achieved by allowing variables of interest (i.e. KBIT-2 and age) to only affect a subset of possible model parameters (combinations of extrinsic, and intrinsic connectivity parameters; shown in Figure 7.3), to identify which model best explained the observed differences in 4-13 Hz power in relation to these variables. Of the seven candidate models, the model allowing for alterations in intrinsic self-inhibition alone was identified as having the greatest model evidence (Figure 7.5A). This model had a free energy difference to the next highest model of 9.1 and a posterior probability of 1 (Figure 7.5B & C), which is considered positive evidence for the model compared to its alternatives (Kass & Raftery, 1995).

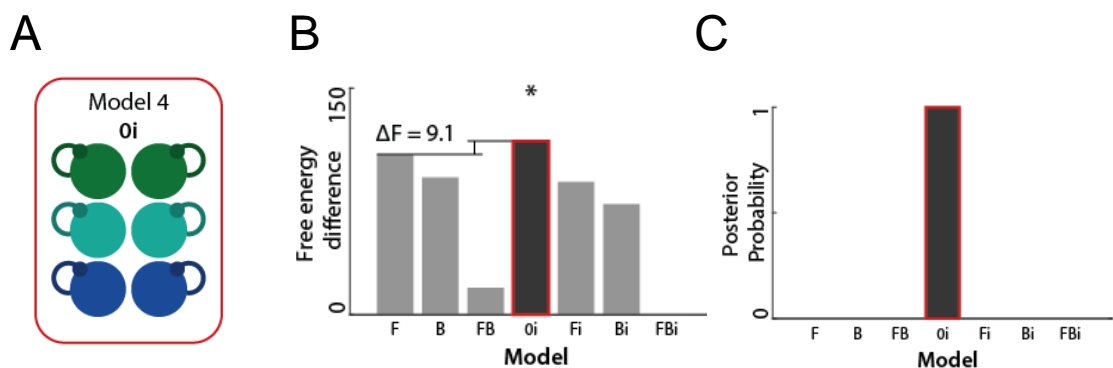


Figure 7.5 Selected model

A. Diagram illustrating the winning network-level model (intrinsic self-inhibition alone). B. Bayesian model comparison showing model evidence (free energy) for each of the seven candidate models: model Oi (model 4; intrinsic self-inhibition alone) shows the highest amount of free energy, with a free energy difference to the next highest model of 9.1. C. Posterior probability of Model Oi shown as 1.

Using the model allowing for changes in intrinsic self-inhibition alone, relationships between raw KBIT-2 score and age with intrinsic self-inhibition were analysed across this network. There was no relationship between age and intrinsic self-inhibition across the network and no significant interaction effect between KBIT-2 score and age (these relationships were zero and therefore are not shown). For raw KBIT-2 score, the biggest effect of KBIT-2 score on intrinsic self-inhibition was seen in right V1. This effect was also estimated with the most certainty (Figure 7.6A; Bayesian confidence

intervals do not cross zero). Relationships between raw KBIT-2 score and intrinsic self-inhibition within this model were also demonstrated within other nodes across the network (left V1, left SPL, left MFG, right MFG), however there is a high degree of uncertainty about parameter values (demonstrated by Bayesian confidence intervals crossing zero) at these locations, and so caution should be taken when considering these true relationships.

Note that whilst Bayesian confidence intervals allow quantification of the certainty with which each parameter is estimated, statistical testing itself is done previously, at the level of different models entered into Bayesian Model Selection, through which the winning network-level model was identified.

The negative relationship between V1 intrinsic self-inhibition and raw KBIT-2 score is further illustrated in Figure 7.6B, showing mean V1 intrinsic inhibition vs raw KBIT-2 score plotted for each subject. This suggests that as raw KBIT-2 score increased, intrinsic self-inhibition in this region decreased. Mean V1 activity is plotted in this figure because the relationship is observed at both occipital poles.

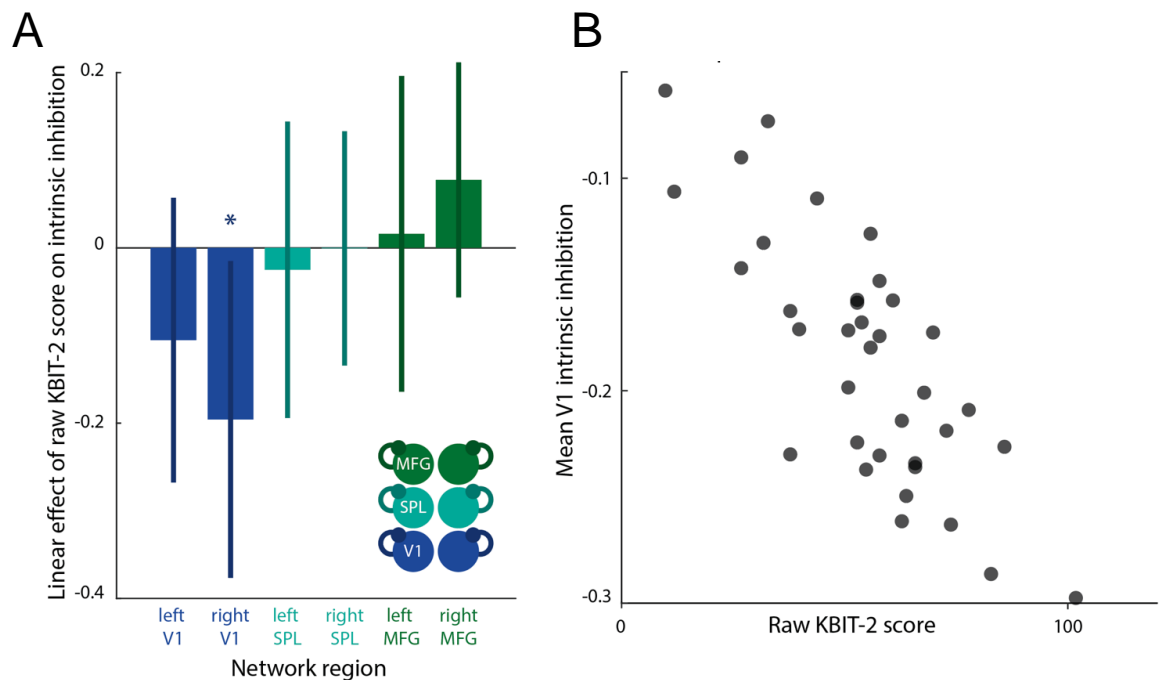


Figure 7.6 Intrinsic self-inhibition

A. Bar chart showing the linear effect of raw KBIT-2 score on intrinsic self-inhibition for each node in the network of the winning model (allowing for changes in intrinsic self-inhibition alone). Bayesian confidence intervals shown here indicate that the effects estimated with most certainty

are located at right V1. B. Scatter graph showing inverse correlation between raw KBIT-2 score and mean V1 (left V1 and right V1 average) intrinsic inhibition of the winning model.

7.4 Discussion

7.4.1 Summary of findings

The primary aim of the chapter was to identify potential neurophysiological mechanisms underlying the association between 4-13 Hz activity and raw KBIT-2 score in adults with DS during EC resting-state recordings. To achieve this, a bilateral model of the alpha network was created. DCM techniques identified intrinsic self-inhibition as the most important model parameter of this network that was associated with KBIT-2 performance. A complex relationship between intrinsic self-inhibition and KBIT-2 score was demonstrated across the network, with negative correlations in occipital and positive correlations in frontal nodes. Due to a large amount of variability in the sample, however, right V1 was the only network node at which the relationship with KBIT-2 had a high level of certainty. Across V1 nodes, there was a strong negative correlation between raw KBIT-2 score and intrinsic self-inhibition. These findings are in line with original hypotheses that inhibition would be the most important parameter associated with KBIT-2 performance, and that there would be a negative relationship between these two variables. No probable relationship between age and intrinsic self-inhibition was demonstrated, despite original hypotheses that age would also be associated with any winning parameters.

Based on these results it appears that, of the network parameters tested, intrinsic self-inhibition within the alpha network is the most important neurophysiological contributor to individual differences in 4-13 Hz activity associated with general cognitive ability in adults with DS. Higher ability is associated with lower intrinsic self-inhibition in right V1. As no probable relationship between intrinsic self-inhibition and age was demonstrated, it is unlikely that age substantially influences intrinsic self-inhibition, or mediates the relationship between KBIT-2 and intrinsic self-inhibition, within the alpha network of this group of individuals.

7.4.2 Research in context

In order to consider the results of this chapter in the context of previous studies it is first necessary to conceptualise the parameter of intrinsic inhibition identified here.

Mechanistically the parameter of intrinsic inhibition describes recurrent self-connections that dampen the excitability of the large projection neurons in the circuitry of the CMC (Figure 7.2). This is a population level summary of intra-laminar local inhibitory populations that connect pyramidal cells within the supragranular or infragranular cortical layers. Less intrinsic inhibition, as seen in V1 with higher KBIT-2, therefore releases the self-suppression of ongoing activity, and results in more excitable cortical sources. It could be hypothesised that reduced inhibition at a cellular level would lead to increased electrophysiological activity in this region, manifesting as release of synchronous alpha activity as measured by EEG (a desirable outcome during eye-closure and indicative of efficient network-level activity control).

This is in accordance with findings in Chapter 6, demonstrating a positive relationship between general cognitive ability and occipital alpha peak amplitude in EC resting-state data. As the presence of an alpha peak is a desirable outcome during eye-closure, potential mechanisms underlying these measures (i.e. intrinsic self-inhibition as identified here) may be indicative of alpha network efficiency, with higher ability individuals able to suppress their visual cortex during eye-closure and individuals of lower ability experiencing impairments in this process.

Considering previous literature, there has been much recent interest in the role of inhibition in DS. The association of higher general cognitive ability with lower intrinsic self-inhibition demonstrated here appears to be in keeping with animal model literature. Specifically in the Ts65Dn mouse model, markers of over-inhibition have been demonstrated, and treatment with pharmacological agents that reduce inhibition (GABA-A receptor antagonists and inverse agonists) have been shown to improve memory deficits in these animals (Braudeau et al., 2011). Markers of over-inhibition that have been demonstrated in Ts65Dn mice include increased number of GABAergic interneurons, enhancement of interneuron excitability, and reduced glutamatergic transmission (Chakrabarti et al., 2007, 2010; Pérez-Cremades et al., 2010; Hernández et al., 2012; Tyler and Haydar, 2013; Guidi et al., 2014; Hernández-González et al., 2015; Contestabile et al., 2017). It is therefore possible that numerous neurobiological factors contribute to a shift in the state of E/I in DS to one of over-inhibition, and conceptually all these factors could influence the parameter of intrinsic self-inhibition identified in this study.

Despite these findings from the Ts65Dn model, the accuracy of this particular animal model is somewhat limited in that it does not contain all the genes implicated in human trisomy 21, and also contains various non-chromosome 21 triplicated genes (Gupta et

al., 2016). It is also noteworthy that although there are numerous mouse models of DS, over-inhibition has not been reported with alternative models (e.g. Dp16; Goodliffe et al., 2016). Moreover findings regarding E/I balance from previous DS research involving humans or human tissue are discordant with Ts65Dn mouse work (detailed below).

Results from a range of human methodologies have indicated that GABAergic inhibition may in fact be reduced in individuals with DS relative to TD controls. Studies using foetal brain tissue or post-mortem tissue, and MRS studies of children, have all reported findings indicative of reduced GABAergic activity in DS. This has included reports of reduced GABA levels, fewer cortical GABAergic neurons, and reduced GABAergic interneuron neurogenesis (Ross et al., 1984; Reynolds & Warner, 1988; Whittle et al., 2007; Bhattacharyya et al., 2009; Smigielska-Kuzia et al., 2010). It is also worth noting the recent drug trial of a GABA inverse agonist in people with DS was unsuccessful in improving cognitive function (Roche, 2016). Although no identified human studies have linked E/I imbalance to cognitive deficits in DS, together these findings may be indicative of reduced inhibition in individuals with DS compared to controls.

As the current study was concerned with differences between individuals with DS and not differences in relation to a control group, it is problematic to compare these findings from previous human studies to the DCM results reported here. What is apparent from the current study, however, is that a non-linear spatial relationship between inhibition and general cognitive ability across the alpha network is present (negative associations occipitally; positive associations frontally). It follows that regional differences in cortical E/I balance may be underlying differences in this relationship. Such regional differences in E/I balance may contribute to discordant findings between studies and suggest the over-inhibition narrative in current DS research may be an over-simplified hypothesis.

7.4.3 Strengths, limitations and future work

This is the first study to examine potential neurobiological mechanisms underlying the relationship between cognitive ability and EEG activity in individuals with DS. The study benefits from only including individuals with genetically confirmed trisomy 21 and the exclusion of individuals with evidence of cognitive decline or dementia. This allowed any pre-decline relationships to be determined.

At present it is unclear if the restriction of probable findings to V1 are indicative of the relationship between cognitive ability and intrinsic self-inhibition only being present in this region, or if instead this is a consequence of inadequate sample size. As discussed in the previous chapter, the EC data analysed here is not from a particularly large sample of individuals. Due to the high degree of variability in the sample, in terms of EEG activity and network parameters investigated, it seems larger studies are warranted to fully elucidate the relationship of ability and intrinsic self-inhibition across the alpha network. It is also unclear why age was not identified as an important factor associated with intrinsic self-inhibition (or mediating the relationship between KBIT-2 and intrinsic self-inhibition), yet significant associations were identified with alpha peak amplitude and age in the previous chapter. DCM studies of older individuals with DS, or larger studies involving participants with a wide range of ages, may be beneficial to fully elucidate the effects of ageing on the network identified here. The use of portable EEG equipment may increase the feasibility of participation for older adults (e.g. by enabling those with mobility issues to participate).

The results reported here indicate that non-invasively measured intrinsic self-inhibition within V1 could be utilised as a potential biomarker of general cognitive ability, which future drug trials in individuals with DS may find useful. In terms of further practical implications, the results presented here demonstrate regionally specific modulation of intrinsic self-inhibition in V1 could be explored as a potential therapeutic target for cognitive enhancement in DS. The seemingly localised nature of these findings, although problematic for pharmacological manipulation, may lend itself to such targeted approaches. For instance, recent research in the TD population has demonstrated the utility of transcranial direct current stimulation (tDCS) in modulating local E/I balance. Specifically, Barron et al. (2016) recently demonstrated that application of tDCS delivered to a discrete cortical region was able to reduce local GABA concentration. Furthermore Barron et al. (2016) demonstrated this method was able to enhance memory by re-expressing otherwise dormant associative memories. In light of the DCM findings demonstrated here, it is therefore possible that such an approach applied to V1 in adults with DS may have beneficial effects on cognitive function, by modulating local E/I balance. However, further research replicating these findings in other DS cohorts, and addressing limitations of the current study, are first necessary before this is explored.

Further to this, although the results here suggest that reducing inhibition in V1 may have potential therapeutic benefits for individuals with DS, it is vitally important to consider that differences in inhibition between individuals with DS may in fact be

compensatory responses to a backdrop of DS neurobiology that is altered relative to TD controls and/or due to AD neuropathology. In this situation, it may be the case that excess intrinsic self-inhibition provides an advantage of some form (for example, reducing seizure-like activity) that counteracts aspects of the DS neurobiological phenotype. A level of caution should therefore be taken when considering intrinsic self-inhibition as a potential therapeutic target in this population. Further studies, focusing on individuals with a history of seizures, may be useful to inform this further.

It is also important to consider that these results are specific to the EC resting-state paradigm through which EEG data was acquired. It is therefore possible that findings are specific to this paradigm and are not indicative of the relationship between general cognitive ability and intrinsic self-inhibition in general. A necessary next step is to model EEG activity from other paradigms (e.g. ERP paradigms) to ascertain whether intrinsic self-inhibition is also linked to cognitive performance in individuals with DS across other forms of neuronal activity.

Additionally, although individuals with cognitive decline were excluded from this study, it is possible that due to the gap between cognitive and EEG testing sessions, some individuals may have begun to experience early cognitive decline (as discussed in the previous chapter). This is also true to some extent for all individuals included in the study, regardless of how close the two sessions were, as decline itself can be difficult to identify. A level of caution should therefore be taken when considering the results presented here as pre-decline. Longitudinal studies, following individuals over several years, are necessary in order to allow a stronger degree of certainty regarding pre-decline classification.

A number of key limitations of this study pertain to those that are specific to DCM methods. For instance, DCM is a method that uses prior information to test competing hypotheses (i.e. which of the parameters tested best explain individual differences in 4-13 Hz activity in relation to KBIT-2 score, given the model). It is therefore possible the prior information is flawed or incomplete, leading to suboptimal nodes or frequencies of interest selected. The prior information utilised here, however, is taken from a range of studies. Additionally prior findings from this thesis – specific to this group of individuals – have been used to inform regions and frequencies of interest. This strengthens the validity of prior information used here for DCM.

A further limitation to consider is that DCM is based on a synthetic representation of the brain, and consequently is limited in its ability to fully replicate the brain in vivo. For

example, the CMC does not contain all cell populations present in the cortex (e.g. glia). Although the activity of such populations is included in the dynamics of forward and backward connections between cell populations encoded within the CMC, hypotheses about these cells (and other variables absent from the CMC) cannot be tested specifically. DCM results should therefore only ever be considered as an approximation to real-world neurobiological activity. In this instance, it remains necessary to obtain further details using alternative methodologies (e.g. MRS).

For any study using DCM to investigate individuals with DS, accuracy of results could be improved by using an observation model (the method that models the effect of head tissues on model-generated electrophysiological signals) that is tailored to individuals with DS. This is because the use of a TD observation model, as in this study, may not accurately reflect the head tissues of individuals with DS where, for example, there are anatomical atypicalities and skull thickness is thinner (Lestrel & Roche, 1979). The DS research community would benefit from the creation of such a model for future research in this area.

It is of interest that the relationship between EEG activity and cognitive ability within individuals with other forms of ID do not appear to have been studied. However, atypical connectivity in theta and alpha bands have been demonstrated in adults with fragile X compared to TD controls (van der Molen et al., 2014). It therefore remains to be determined whether findings reported here are unique to individuals with DS or are instead related to ID in general. Future research using DCM in non-DS ID populations are necessary to clarify this.

7.4.4 Conclusions

DCM of alpha network activity in EC resting-state EEG data indicates that intrinsic self-inhibition is the most important neurophysiological parameter (of those tested) mediating the relationship between 4-13 Hz EEG activity and individual differences in general cognitive ability in adults with DS. On further examination, there appears to be a strong negative relationship between this parameter and general cognitive ability in occipital regions. Potential mechanisms underlying differences in intrinsic self-inhibition are as yet unclear but may relate to changes in GABAergic interneurons, as indicated by mouse model work. Differences in intrinsic self-inhibition may in turn impact on alpha network efficiency.

Larger studies utilising a range of EEG paradigms are necessary to fully elucidate the relationship between intrinsic self-inhibition and general cognitive ability across the alpha network and within different networks (e.g. those underlying ERP activity) in this population. Future studies may also benefit from recruiting an older cohort of individuals with DS to further examine ageing effects.

Results of this study indicate that the parameter of V1 intrinsic self-inhibition (as obtained by DCM) has potential as an electrophysiological biomarker of general cognitive ability in adults with DS. Furthermore, it is possible that targeted interventions aimed at reducing local V1 GABA levels (e.g. tDCS) could have beneficial effects on cognition in this population.

Chapter 8 Overall discussion

8.1 Overall summary of key findings

Findings in relation to specific aims and hypotheses are discussed within each chapter. Provided here is a summary of key findings relating to each primary aim of this thesis, of which there were four:

- i) To investigate the feasibility and generalisability of resting-state EEG recordings in adults with DS;
- ii) To identify differences in EC resting-state EEG activity between adults with DS (with no evidence of cognitive decline or diagnosis of dementia) and TD age- and sex- matched control subjects;
- iii) To investigate how EEG spectral measures obtained during EO and EC resting-state recordings are related to age and general cognitive ability in adults with DS (with no evidence of cognitive decline or diagnosis of dementia);
- iv) To investigate potential cortical circuitry underlying EEG oscillations of interest using DCM.

8.1.1 Aim 1: Feasibility and generalisability of resting-state EEG recordings

In regard to feasibility and generalisability of resting-state EEG studies in individuals with DS, findings suggest the overall sample of participants taking part in this EEG study had greater general cognitive ability when compared to a larger DS sample. Analysis revealed that this bias was introduced at the level of invitation to participate in the study. Additionally, the age of participants was younger than the larger DS sample from which they were recruited. Analysis revealed this was due to older individuals being less likely to agree to participate once they had been invited to take part in the EEG study. Further research is necessary to identify potential barriers to older adults with DS participating in EEG research.

Furthermore, findings from this particular chapter (Chapter 4) were concerned with the total sample that consented to take part in the overall EEG study, in order to inform broadly about EEG research in this population. This overall sample included individuals with cognitive decline and dementia. Due to additional exclusion criteria applied for subsequent chapters, this initial bias in terms of age and ability is therefore likely to be further exacerbated for each participant sub-population used within individual chapters

(e.g. due to the exclusion of individuals with cognitive decline or a diagnosis of dementia). Together these results suggest caution should be taken when generalising the results of this thesis to individuals with DS with more severe ID or older individuals with DS.

It was also found that splitting the EC recording did not reduce movement artifacts in the data, however this approach may still be beneficial in terms of reducing drowsiness. Evidence that this approach may have reduced participant drowsiness was provided by analysis within Chapter 5 (see section 5.4.2) detailing DS vs. control analyses. In this analysis theta power was significantly increased in participants with DS who underwent the full-block compared to split-block EC paradigm. According to previous research, this may indicate increased drowsiness associated with the full-block recording paradigm.

8.1.2 Aim 2: differences in EEG activity between adults with DS and matched TD controls

Chapter 5 aimed to characterise differences in EEG activity between adults with DS and matched TD control subjects. Significant differences between groups were identified across all bands investigated. Overall results indicate that individuals with DS have an EEG spectrum that could be described as “slower” than that belonging to matched TD control subjects: delta and theta power values were significantly higher whereas alpha and beta power values were significantly lower in adults with DS (only EC data examined). This pattern of findings was true for both occipital and frontal regions. Alpha band oscillations in particular exhibited strong group differences.

Also illustrated by the results of this chapter is the potential utility of analysing topographical differences in EEG activity: although the overall pattern of findings was similar for occipital and frontal regions, differences were identified (notably alpha and beta power were significantly lower in individuals with DS compared to TD controls in the occipital region, however in the frontal region these group differences failed to reach significance). The potential utility of analysing both absolute and relative power values in EEG studies in this population was also demonstrated.

The key findings of this chapter summarised above are in line with original hypotheses (see section 2.5.2). However, beta power was hypothesised to be higher in individuals with DS and instead was found to be lower. Although this finding was unexpected, it is

in accordance with the theory that individuals with DS have an “slower” EEG spectrum compared to TD controls.

8.1.3 Aim 3: EEG measures related to age and general cognitive ability

Chapter 6 aimed to investigate how individual differences in EEG measures were related to individual differences in general cognitive ability and age between adults with DS. Significant relationships between these variables in both EO and EC resting-state paradigms were demonstrated.

In EO recordings increasing age was associated with increased occipital alpha activity (power in addition to peak amplitude) and increased frontal beta power. Additionally, in EO recordings higher frontal delta power was associated with higher KBIT-2 score. In EC recordings, increasing age was associated with decreased frontal delta power and increased alpha peak amplitude in both regions investigated. Additionally, in EC recordings higher alpha peak amplitude was associated with higher KBIT-2 score in both regions, and higher theta power was associated with higher KBIT-2 score in the frontal region. It was concluded that EC theta-alpha (i.e. 4-13 Hz) activity may be particularly associated with general cognitive ability in adults with DS, and as such further investigation of the network underlying this activity may be valuable.

Overall the key findings of this chapter summarised above are not in line with original hypotheses (see section 2.5.2). No correlations between EEG variables and general cognitive ability were expected in EO data. Consequently, associations between frontal delta power and KBIT-2 score were unexpected. Both lower general cognitive ability and increasing age were expected to be associated with power measures indicative of EEG slowing, and lower alpha peak amplitude. In line with this, alpha peak amplitude was found to be positively associated with general cognitive ability, however this measure was also found to increase with increasing age. Power measures indicative of EEG slowing were not associated with lower general cognitive ability or age. Instead, greater activity in low frequencies (delta and theta) were associated with greater general cognitive ability, and increasing age was associated with lower delta power and increased alpha and beta power.

8.1.4 Aim 4: Potential cortical circuitry underlying 4-13 Hz activity associated with general cognitive ability and age

The final data chapter investigated potential neurophysiological mechanisms underlying 4-13 Hz EC EEG activity in relation to raw KBIT-2 score and age in adults with DS (i.e. potential mechanisms underlying relationships demonstrated in Chapter 6). DCM of the alpha generating network demonstrated intrinsic self-inhibition was the key network parameter underlying observed differences in 4-13 Hz power in relation to KBIT-2 score across participants. In particular occipital intrinsic self-inhibition was negatively correlated with general cognitive ability. No probable effects of age were seen across the network. It was suggested that the parameter of intrinsic self-inhibition at V1 has potential as an electrophysiological biomarker of general cognitive ability in adults with DS, and that interventions aimed at reducing V1 inhibition may have a positive impact on cognitive ability in this population.

The key findings of this chapter summarised above are in line with original hypotheses (see section 2.5.2).

8.2 Overall interpretation of findings

As outlined in the rationale for this study (see section 2.5), enhancing cognitive ability in individuals with DS may be achievable through the understanding of factors underlying individual differences in cognition within this population, and from this identifying potential targets for cognitive enhancement. Underlying this premise is that abilities vary greatly between individuals with DS, despite all having an extra copy of chromosome 21. EEG allows the exploration of brain activity associated with these individual differences in cognition and, when combined with modelling techniques such as DCM, potential neurophysiological factors underlying these associations to be elucidated.

The current thesis has identified a range of EEG measures associated with general cognitive ability and age in this sample of individuals with DS. From these findings, intrinsic inhibition has been identified as a potential neurophysiological factor underlying individual differences in general cognitive ability.

Due to the inclusion of a chapter comparing EEG spectra from individuals with DS to that from TD controls, it is possible to conclude that although some EEG characteristics of higher ability individuals with DS appear to be closer to that of TD controls, other EEG characteristics associated with higher ability are of the opposite direction. For example, EC peak amplitude was significantly lower in individuals with DS compared to TD controls, and when analysed within individuals with DS, higher peak amplitude was

associated with higher KBIT-2 score. Therefore, it appears of benefit to individuals with DS for this variable to be closer to TD levels. In contrast, EC theta power was significantly higher in individuals with DS compared to TD controls, yet in the following chapter greater EC theta power correlated with greater KBIT-2 score in individuals with DS. Consequently it appears of benefit in individuals with DS for this EEG variable to be further away from TD levels.

Taken together these results indicate it is not necessarily that higher ability individuals with DS have EEG spectra closer to TD spectra. The implications of this are that a treatment approach aimed at “normalising” the overall EEG spectra in individuals with DS (i.e. 0.5 - 30 Hz) may have negative consequences. Based on the findings of this thesis it appears targeting EEG variables that are associated with individual differences in cognitive ability in DS, instead of focusing on EEG variables that differ between individuals with DS and TD controls, may be a worthwhile approach to future studies investigating cognitive enhancement. Furthermore, the results presented in this thesis suggest that a shift in E/I balance towards increased inhibition may be associated with cognitive impairment in individuals with DS. The results also suggest, however, a simple narrative of “over-inhibition” in DS may be inadequate. Instead it is possible relationships between E/I balance and cognitive ability differ between regions, as indicated by the potential positive associations between frontal intrinsic inhibition and general cognitive ability demonstrated in Chapter 7. More research is needed to explore this hypothesis further.

In terms of secondary aims that were explored in this thesis (detailed within individual experimental chapters), results have provided key methodological information in relation to EEG study design in this population. Recommendations include EC paradigms that are not a single recording block, and obtaining both EC and EO data where possible. Utilising both absolute and relative EEG measures for analysis is also recommended when comparing individuals with DS to TD controls. Furthermore, targeted and supported recruitment, and/or the use of portable EEG equipment may be beneficial for DS studies where severe ID, ageing, or dementia are key participant variables to be investigated.

8.3 Overall research in context

The field of research reporting the use of EEG in individuals with DS is relatively small. Results span many decades, utilising different methods, and convergent evidence is weak. Despite this, differences in alpha activity between individuals with DS and TD

controls, and the relationship between this activity and cognitive ability within individuals with DS, is indicated within the literature on a fairly consistent basis. Evidence supporting the hypothesis that individuals with DS have a “slower” EEG spectrum compared to TD controls is also relatively consistent.

The current study adds further evidence to the existence of a slower EEG spectrum in individuals with DS compared to TD controls, and for the importance of alpha activity (including extended-alpha; 4-13 Hz) in this population. This study adds to this knowledge by investigating the relationship between a range of EEG measures in relation to general cognitive ability and age in a population of adults with DS free from evidence of cognitive decline, and by modelling potential neurophysiological mechanisms contributing to these findings. The current study also suggests the previously unidentified EEG variable of EO frontal delta activity may be an important factor relating to cognitive ability in DS.

The use of DCM methods and the identification of intrinsic self-inhibition as a key parameter associated with general cognitive ability informs both human and animal research in DS. Research linking these fields is vital for the progression of our understanding of DS and for finding treatments targeting ID in this population. This particular key finding is especially important due to the conflicting findings between human and animal studies regarding E/I balance at present, and therefore informs this further by corroborating findings from the Ts65Dn mouse, which have indicated that over-inhibition may be linked to cognitive impairment in DS.

Results presented here also indicate that EEG methods are particularly suited for establishing and exploring links between individuals with DS and DS mouse models. As oscillatory brain activity is well conserved across mammals (Buzsáki, et al., 2013), electrophysiological studies of DS mouse models may be valuable. However, the ultimate role of such experiments is to screen drugs for their potential safety and efficacy in humans. It is therefore important to note that there are numerous pharmacological compounds that have been shown to influence theta-alpha activity in humans, and that already have well established safety profiles. These include the stimulants nicotine (Foulds et al., 1994) and caffeine (Siepmann & Kirch, 2002), in addition to a range of licensed psychotropic medications (Aiyer et al., 2016). The current study indicates that not only the exploration of the effects of these drugs on cognition in individuals with DS is warranted, but also that care should potentially be taken with their prescription in this population (for example, the common

antidepressant paroxetine and anticonvulsant valproate have both been shown to reduce alpha activity).

Additionally, age effects on EEG measures were extensively explored and in particular indicated the utility of EO resting-state paradigms for investigating age-related changes. Findings suggest power changes may occur in some bands across adulthood (e.g. delta), whereas power increases in other bands may only be associated with older age (e.g. alpha and beta). The concept of alterations across the EEG spectrum with increasing age in DS (e.g. slowing) is therefore likely to be complex, with different bands experiencing changes in different timeframes. Also indicated is that age-related changes in EEG activity may differ for EO and EC measures, and/or between frontal and occipital regions (e.g. EO alpha peak amplitude may increase across adulthood, whereas EC alpha peak amplitude may only show increases with older age). These specific age-related changes have not previously been explored in DS and together indicate such an approach may be useful for identifying the influence of delayed maturation and ageing processes on brain activity in this population.

8.4 Remaining questions and future directions

8.4.1 Concept of general cognitive ability

The focus of this thesis is on general cognitive ability as indicated by raw KBIT-2 score. Although widely utilised as a measure of general cognitive ability within DS research (see section 1.3.3.1), the concept of general cognitive ability as a definable and measurable feature of an individual is not without its criticisms. Namely other forms of intelligence – for example those relating to creativity, emotion and practical skills – are not encompassed by this measure, and are therefore excluded from the overall concept of general cognitive ability used in this study. Future studies may benefit from using an alternative general measure of ability that relates more to everyday skills (e.g. an adaptive behaviour scale), or devising a composite score from a range of ability tests. An alternative approach would be to utilise measures pertaining to specific cognitive domains (e.g. verbal ability, memory, attention), which are clearer concepts to define and measure. However, a strong association between such tests has been demonstrated in this population (Startin et al., 2016). It is therefore unlikely findings related to specific domains would have substantially differed to those reported here.

8.4.2 Influence of other variables

Key questions remaining from this research pertain to the effects of age and decline, in addition to more specific hypotheses regarding the genetic effects, e.g. of APOE on EEG variables and relationships with cognitive ability. Larger studies and/or targeted recruitment will provide information in answer to these questions.

The influence of potential covariates of general cognitive ability – such as years in education or socioeconomic status – have also not been investigated in this study. The analysis presented here is therefore missing potentially important information about whether and how such variables play a role in the mechanisms discussed. For example, there is evidence from the TD population that socioeconomic status may affect resting-state networks (Sripada et al., 2014). Future studies may therefore benefit from further investigation of these factors.

Additionally, EEG variables obtained through alternative EEG paradigms (e.g. ERP studies) and their associated networks require investigation to determine whether results reported here are specific to resting-state activity. It is therefore necessary for future studies to incorporate additional EEG paradigms into the recording session.

8.4.3 Exploration of delta activity

Due to the indication of delta being related to cognition it would be worthwhile for future studies to explore this further, possibly through similar DCM techniques as used here for 4-13 Hz oscillations. However, cortical delta networks are less well defined within previous literature compared to alpha networks, and so the accuracy and validity of any findings would be poorer. Combined EEG and fMRI studies may help to identify specific nodes underlying delta activity in individuals with DS, which could then allow the delta generating network to be explored using these techniques. Combining EEG and MRI studies in this way may also improve the accuracy of alpha network nodes selected in the current study.

8.4.4 Lifespan analysis

Linking the findings of this thesis to findings in infants and children with DS is also warranted. Although EC resting-state paradigms cannot be used in babies and young children, as EO findings have also been identified here it may be possible to investigate the relationship between delta power and cognitive ability in this younger

population through this resting-state paradigm. Linking adult and infant work in this way will help elucidate developmental effects on EEG variables and the effects of development on any relationship between these variables and cognition. The EO paradigm used in this study was designed to allow results between adult and infant streams within the larger LonDownS project (described in section 3.1) to be linked, and so this is therefore achievable in the short-term.

8.4.5 Cognitive impairment in the TD population

Furthermore, a wider research question that remains to be answered is how the findings of this thesis relate to EEG variables that have been linked to impaired cognition occurring within the TD population. Specifically, the finding of a slower EEG spectrum in individuals with DS (Chapter 5) is linked with both AD and MCI within the TD population (see section 2.3). It is therefore possible that cognitive impairment has the same EEG signatures regardless of whether this is due to ID or neurodegenerative disease.

Alternatively, it is possible that early amyloid deposition within individuals with DS has influenced the EEG measures obtained in this study. Due to the high likelihood of amyloid being present in the brains of some participants with DS in this study, it is difficult to determine to what extent the results of this thesis may be influenced by this. Attempts were made to minimise the potential confounding presence of significant AD neuropathology by excluding individuals with presence of cognitive decline, however this approach is limited in that amyloid deposition has been shown to occur from childhood in DS (Lemere et al., 1996). It is therefore possible that EEG measures associated with age in this study are confounded by the presence of amyloid pathology.

Studies combining EEG with imaging methods that are able to assess amyloid deposition (e.g. PET) are necessary to explore this further. Additionally, the inclusion of a group of individuals with DS with cognitive decline and/or a dementia diagnosis would allow it to be determined whether age-related EEG changes established here in individuals without decline are amplified in individuals with decline/dementia, or whether instead alternative EEG changes are demonstrated in this group.

Similar studies to this, involving other populations of individuals with ID (e.g. fragile X), would also be beneficial. This would enable it to be determined whether the findings

presented here are unique to individuals with DS or are instead associated with low cognitive ability in general.

8.4.6 Drug exploration

As a further future direction, it is important to note that DCM techniques can be used to model the effects of specific pharmacological compounds on the network and parameters identified here. For instance, the effect of specific GABA receptor antagonism on intrinsic self-inhibition and EEG spectral features within this population could be investigated. It is possible that such an approach may improve drug discovery.

This thesis has provided an in-silico model (i.e. described a synthetic neural network with specific variables of this network associated with general cognitive ability in DS) in which the potential influence of such compounds in DS can be explored. An example of a specific hypothesis that could now be tested is whether the unsuccessful GABA-A receptor antagonist developed by Roche exerts any effects on intrinsic self-inhibition in this model, and if so where these effects are strongest. In addition, alternative GABA-A targeting drugs could be tested.

The addition of computational models capable of replicating human DS brain activity to our range of DS research methodology may enhance this field in the same way as the addition of animal models in the previous century. Future work should therefore focus on the further development of such models over the lifespan of individuals with DS.

8.4.7 Ethical implications

It would be inaccurate to label the brain of an individual with DS (prior to significant AD neuropathology) as “unhealthy”, simply because of the presence of an extra copy of chromosome 21. Level of functioning, however, is impaired in individuals of DS compared to individuals of the TD population, and risk for dementia in older adults is greatly increased. As a consequence of this, enhancing level of functioning is an underlying theme in this study, and in DS research in general.

However, an important ethical consideration is for whom cognitive enhancing “treatment” (prior to cognitive decline) in DS would be of benefit to. Recently research investigating other neurodevelopmental disorders has come under scrutiny for their attempts to cure symptoms that, for many individuals with these disorders, are not felt

to be problematic (e.g. impairments in social communication in individuals with autism; Jaarsma & Welin, 2012). There is currently a movement – termed the neurodiversity movement – which seeks to prevent such natural variation from being pathologised and instead seeks acceptance for individuals who are not “neurotypical”.

From the outside it seems logical that enhancing cognitive ability would improve the lives of individuals with DS, however this assumption may be misplaced. Qualitative studies involving individuals with DS and their families may help to investigate this further. Moreover, the wider societal implications or further reducing such neurodiversity may lead to enhanced stigma for individuals who are unable to or who choose not to have treatment for ID. I do not believe these are reasons to not undertake such research, however the DS research community would benefit from involving individuals with DS and their families in research strategy to identify what they themselves would like to be the main aims of our work.

8.5 Conclusions

Overall this thesis has demonstrated the utility of simple resting-state EEG paradigms for investigating individual differences in adults with DS. Findings enhance our understanding of neural factors associated with individual differences in general cognitive ability. Potential approaches aimed at targeting these factors for the purpose of cognitive enhancement in this population have been proposed. Future research recommended in this thesis will not only improve our knowledge of DS but will likely also enhance our understanding of neural processes underlying cognitive ability and cognitive impairment across all individuals.

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Appendix

Cognitive assessment protocol: Startin et al., 2016.....	202
Cognitive assessment consultee information sheet	223
Cognitive assessment role of consultee information sheet	228
Cognitive assessment participant information sheet	230
Cognitive assessment consultee consent form	242
Cognitive assessment participant consent form	245
EEG assessment consultee information sheet.....	252
EEG assessment participant information sheet.....	256
EEG assessment consultee consent form.....	265
EEG assessment participant consent form.....	268

Cognitive assessment protocol: Startin et al., 2016

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The LonDownS adult cognitive assessment to study cognitive abilities and decline in Down syndrome

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Abstract

Background: Down syndrome (DS), the most common genetic cause of intellectual disability, is associated with an ultra-high risk of developing Alzheimer’s disease. However, there is individual variability in the onset of clinical dementia and in baseline cognitive abilities prior to decline, particularly in memory, executive functioning, and motor coordination. The LonDownS Consortium aims to determine risk and protective factors for the development of dementia and factors relating to cognitive abilities in people with DS. Here we describe our cognitive test battery and related informant measures along with reporting data from our baseline cognitive and informant assessments.

Methods: We developed a cognitive test battery to assess general abilities, memory, executive function, and motor coordination abilities in adults with DS, with informant ratings of similar domains also collected, designed to allow for data on a broad range of participants. Participants (n=305) had a range of ages and abilities, and included adults with and without a clinical diagnosis of dementia.

Results: Results suggest the battery is suitable for the majority of adults with DS, although approximately half the adults with dementia were unable to undertake any cognitive task. Many test outcomes showed a range of scores with low floor and ceiling effects. Non-verbal age-adjusted IQ scores had lower floor effects than verbal IQ scores. Before the onset of any cognitive decline, females aged 16-35 showed better verbal abilities compared to males. We also identified clusters of cognitive test scores within our battery related to visuospatial memory, motor coordination, language abilities, and processing speed / sustained attention.

Conclusions: Our further studies will use baseline and longitudinal assessments to explore factors influencing cognitive abilities and cognitive decline related to ageing and onset of dementia in adults with DS.

Key words

Down syndrome, intellectual disability, Alzheimer’s disease, dementia, cognition, memory, executive function, motor coordination

Introduction

Down syndrome (DS) is the most common genetic cause of intellectual disability (ID) and is caused by the presence of an additional chromosome 21. DS has a UK incidence of approximately 1 in 1000 live births (Wu and Morris 2013). The life expectancy for individuals with DS has risen dramatically over the previous 50 years; a recent study estimated current life expectancy to be almost 60 (Englund *et al.* 2013). With this increase in life expectancy it has become apparent DS is associated with an ultra-high risk of developing Alzheimer's disease (AD) compared to typically developing individuals (Wiseman *et al.* 2015). A recent study estimated lifetime risk for dementia based on cumulative incidence may be as high as 95.7% by age 68, with an age-related increase from 26.1% at age 50 (McCarron *et al.* 2014).

This increased risk of dementia is thought to be largely due to the overexpression of genes on chromosome 21. Of particular interest is the amyloid precursor protein (*APP*) gene, mutations in which have been associated with early onset AD in the typically developing population. Deposits of amyloid, a characteristic feature of AD and encoded by the *APP* gene, are reported to be present in the brains of almost all adults with DS with full trisomy 21 over the age of 30 (Mann 1988, Wisniewski *et al.* 1985). Despite this, there is considerable variability in the clinical presentation and age of onset of dementia in DS; some adults receive a dementia diagnosis before age 40 while others do not show signs of dementia until they reach their 60s, with a mean age of diagnosis of 55 (Coppus *et al.* 2006, Holland *et al.* 1998, Margallo-Lana *et al.* 2007, McCarron *et al.* 2014, Tyrrell *et al.* 2001). This wide variability suggests there are a number of risk factors for the development of clinical dementia in addition to *APP* overexpression, as well as protective factors against its development.

Dementia in DS develops on a background of an altered cognitive profile. Later developing brain networks, including the prefrontal cortex (PFC), hippocampus, and cerebellum, have been suggested to be most affected in DS (Edgin 2013). Structural MRI studies have reported smaller brain volumes in these regions in DS before the onset of AD (Aylward *et al.* 1999, Beacher *et al.* 2010, Carducci *et al.* 2013, Pinter *et al.* 2001a, Pinter *et al.* 2001b, Teipel *et al.* 2003), and delayed hippocampal myelination has been demonstrated (Abraham *et al.* 2012). In addition, altered frontal functional connectivity (Anderson *et al.* 2013, Pujol *et al.* 2015) and white matter integrity (Powell *et al.* 2014) have been reported in DS. Those with dementia show further reduction in hippocampal volumes (Aylward *et al.* 1999, Beacher *et al.* 2009) and decreased frontal white matter integrity (Powell *et al.* 2014) compared to those without dementia.

Altered development of the PFC, hippocampus and cerebellum in DS is supported by studies reporting related cognitive impairments, specifically in executive function, memory and motor coordination respectively. Individuals with DS show impaired executive functioning abilities compared to both mental age (MA) matched typically developing controls and individuals with non-DS ID (Lanfranchi *et al.* 2010, Rowe *et al.* 2006), although one aspect of executive functioning, working memory, has been reported not to be affected in DS compared to MA controls (Pennington *et al.* 2003). Both verbal and visuospatial memory have been reported to be impaired in DS compared to MA controls (Pennington *et al.* 2003), in particular as memory load increases (Visu-Petra *et al.* 2007). It has further been suggested individuals with DS show relatively poorer verbal compared to visuospatial memory (Baddeley and Jarrold 2007, Jarrold *et al.* 2002, Lanfranchi *et al.* 2012), and visual object memory is more impaired than visual spatial memory (Vicari *et al.* 2005). Finally, individuals with DS have been reported to show slower motor responses compared to MA controls (Edgin *et al.* 2010, Frith and Frith 1974). Although these general profiles of cognitive abilities are found for individuals with DS at the group level, there is a large variability both across and within individuals in cognitive profiles.

This cognitive profile in DS has been proposed to affect the presentation of dementia symptoms. Decline in frontal function (Holland *et al.* 1998, Holland *et al.* 2000), characterised by executive function impairments (Adams and Oliver 2010, Ball *et al.* 2008) and behavioural and personality changes (Ball *et al.* 2006, Dekker *et al.* 2015), has been implicated as an early dementia-related change in DS. Memory impairments, usually associated with AD in the general population, are also found in adults with DS and dementia (Ball *et al.* 2006, Kittler *et al.* 2006), with changes in praxis occurring later (Dalton *et al.* 1999).

Concept and aims

The London Down Syndrome Consortium (LonDownS) aims to identify risk and protective factors for the development of the clinical signs of dementia in DS. This will inform understanding of the development of AD and identify potential mechanisms as well as predictive phenotypes. We also aim to establish the pre-dementia cognitive profile of adults with DS, allowing us to identify factors relating to cognitive abilities. This will help to inform interventions to influence developmental trajectories across the lifespan. Our study therefore requires detailed cognitive assessments that allow for data on the broadest range of participants possible in terms of age and abilities, with minimal floor and ceiling effects. We also took into account the typical cognitive difficulties in this population, such as expressive language impairment, as well as co-morbidities such as hearing and vision problems. We therefore compiled a cognitive assessment battery requiring minimal verbal responses and using informant ratings of similar domains.

Here, we describe the LonDownS cognitive test battery for adults with DS, and provide data on baseline cognitive and related informant assessments.

Methods

Participants

Cohort 1: adults aged 36 years and over

We have recruited and completed baseline assessments for 181 adults aged 36 years and over, with (n=51) and without (n=130) a clinical diagnosis of dementia, with longitudinal assessments planned to assess cognitive decline. Longitudinal assessments are essential to assess cognitive decline in individuals with DS due to the presence of an ID potentially confounding test results. Two additional adults were assessed then excluded from analyses after genetic testing revealed no additional chromosome 21, mosaicism or translocation. One further adult withdrew after starting the initial assessment.

Cohort 2: adults aged 16-35 years

We have recruited and assessed 124 adults aged 16-35 years. These adults have initially been assessed once, to explore cross-sectional cognitive profiles of individuals with DS before the onset of dementia.

Recruitment

Participants were recruited across England and Wales (focusing on the Greater London area and South East England) via local care homes, DS support groups and existing participant databases. We also established a network of National Health Service (NHS) Trust sites to identify and approach potential participants. Participants were given a gift voucher as compensation for their time, and we reimbursed all travel expenses.

Inclusion and exclusion criteria

All participants were required to have a clinical diagnosis of DS. This was confirmed genetically using saliva or blood samples. We excluded participants with an acute physical or mental health condition, although when such participants recovered they were eligible for the study.

Ethical approval and consent

Ethical approval was obtained for the LonDownS study from the North West Wales Research Ethics Committee (13/WA/0194). Participants with and without the capacity to consent were able to participate. Where individuals had capacity to consent we obtained written informed consent. Where individuals did not have capacity to consent a consultee was appointed and asked to sign a form to indicate their decision regarding the individual's inclusion based on their knowledge of the individual and his/her wishes, in accordance with the UK Mental Capacity Act 2005.

Assessment battery

Our battery was based on several established and novel assessments relevant to the cognitive profile and development of dementia in DS, including the Arizona Cognitive Test Battery (ACTB) (Edgin *et al.* 2010) which includes several computer tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (CANTAB® 2016). The ACTB was developed to assess a range of skills relevant to those brain areas most affected in DS, to have variable scores with low floor effects that are suitable for a range of ages and contexts, to be suitable for a non-verbal population, and to show good test-retest reliability. This battery was validated using individuals with DS aged 7-38. However, our previous pilot work showed some components of the ACTB had significant floor effects in older adults aged 45+ with DS, and some tests forming part of the battery were not able to distinguish between those with and without dementia (Sinai *et al.* 2016).

We therefore made several modifications to the ACTB. We excluded some tests for older adults (Cohort 1) based on our pilot results, specifically the virtual generated arena, cats and frogs, and finger sequencing. We added comparable table-top tests as our previous studies have supported their use in people with DS and found lower floor effects compared to computer tasks (Sinai *et al.* 2016). We also added informant-rated tools to cover similar cognitive domains as the neuropsychological test battery, allowing us to collect data on those unable to engage in cognitive testing.

A summary table of assessments can be found in the Supplementary material S1.

Test administration

To avoid excessive burden to participants who were unable to engage in formal assessment and follow simple instructions (e.g. those with more severe dementia) the battery was only administered to those who were able to understand, meet thresholds for, and respond to the Kay vision test (Kay 1983), the Whisper hearing test (Prescott *et al.* 1999) and the first question of the KBIT-2 (Kaufman and Kaufman 2004). Adults who did not meet these thresholds did not complete any further tests in the battery, though their carers completed all informant questionnaires. In addition, we used the motor screening task (MOT) from the CANTAB (CANTAB® 2016) to familiarise participants with using the touchscreen. For this participants were required to press a cross on the screen at different locations for 10 trials.

Task order was counter-balanced across participants (see Supplementary material S2). We used a fixed order, but took a pragmatic approach that allowed flexibility where necessary. The assessment was completed in one session where possible, approximately 3 hours in duration, with a 10 minute break in the middle and additional breaks as necessary. Assessments took place where convenient for participants, usually in their homes, and occasionally using our testing rooms. Notes about the participant's attention, co-operation, affect, and anxiety were made where appropriate throughout the assessment, including reasons for non-completion of tasks.

Vision and hearing assessment

Kay vision test

Participants' visual acuity, wearing correction if appropriate, was tested using the Kay vision test (Kay 1983). Participants were asked to identify increasingly small pictures from 3m away, verbally or by pointing to the screening card, and the smallest size the participant could see was recorded. A threshold of 3/19 was used to identify those with significant vision problems that would invalidate cognitive test results. Only participants who met this threshold were administered further cognitive tasks.

Whisper hearing test

Participants' hearing abilities, using correction if appropriate, were tested using the Whisper test (Prescott *et al.* 1999), adapted for individuals with ID. The researcher stood behind the participant, 50cm from the midpoint between the ears on the top of the head, and whispered the name of one of eight objects (toothbrush, popcorn, ice cream, snowman, reindeer, hotdog, football, seesaw) displayed on the participant's test card. Words were simple spondee words, i.e. contained two syllables with equal stress on each. The participant was asked to repeat the word or point to the correct picture. If the participant was unable to hear a whispered word a conversational, then loud voice, was used. The quietest level heard was recorded. Only participants who were able to hear and respond correctly to at least a loud voice were administered further cognitive tasks.

Test of general abilities

KBIT-2

We assessed general cognitive abilities using the Kaufman Brief Intelligence Test 2 (KBIT-2) (Kaufman and Kaufman 2004). The KBIT-2 consists of three subtests, two of which assess verbal IQ (verbal knowledge and riddles) and one assessing non-verbal IQ (matrices). Each subtest was started at item 1, and stopped after 4 consecutive incorrect answers. The KBIT-2 provides raw scores or age-dependent IQ scores. As we expected significant floor effects for IQ scores (i.e. an IQ of 40), we used raw scores as the main measure of general ability.

Tests of memory

CANTAB – PAL

The paired associates learning (PAL) task is a measure of visuospatial short-term memory from the CANTAB (CANTAB® 2016). Participants were required to remember locations of an increasing number of patterns in progressive stages, hidden behind boxes on the screen. If a particular stage was not completed in a maximum of 10 attempts the test terminated. The main outcome from this test was the first trial memory score: the number of pattern locations correctly remembered on the first trial for each stage attempted. The secondary outcome was the number of stages completed.

CAMCOG – delayed incidental memory, verbal fluency and orientation

The Cambridge Cognitive Examination (CAMCOG) is a series of neuropsychological tests from the Cambridge Mental Disorders of the Elderly Examination (CAMDEX), used to assess cognitive impairments associated with dementia (Roth *et al.* 1986), and adapted to assess cognitive abilities in people with DS (Hon *et al.* 1999). The three tests used in our battery assess short-term memory (delayed incidental memory), frontal function (semantic verbal fluency) and participants' knowledge of when it is (i.e. the day, month and year) and where they are (orientation).

Firstly, participants were administered the picture naming task, in which they were shown 6 pictures of objects and asked to name them. There were then two distractor tasks before incidental memory was tested: the verbal fluency task (see under tests of executive function) and the orientation task, in which participants were asked their full name, the day of the week, the month, the year, where they are, and the nearest city / town. For the orientation task the outcome is calculated from the number of questions answered correctly, with fewer points given if a clue was required. Finally, the delayed incidental memory task required participants to freely recall the pictures they saw earlier, then recognise them from 3 options. The outcomes for the incidental memory task were the number of objects correctly recalled and recognised.

Delayed object memory

This test is a measure of short-term memory, based on the Fuld object memory test (Fuld 1980). We adapted this task to use 7 objects (toothbrush, comb, spoon, pencil, watch, coin and key) rather than 10 to reduce the memory load for participants. We also added a delayed memory trial (5 minute delay) in addition to two immediate memory trials to assess delayed as well as immediate memory. At the start of each trial participants named all seven objects and were instructed to remember them; any objects not

correctly identified were named by the examiner. Participants' memory was tested during two immediate recall trials followed by one 5-minute delayed recall trial. Immediately following each recall trial any objects not remembered were shown to the participant. During the delay wherever possible we collected physical measurements (height, weight, abdominal / head / neck circumference, gait, blood pressure, and pulse) from the participant. The outcome measures were the total number of objects correctly remembered in the two immediate memory trials combined and in the delayed memory trial.

NAID - memory for sentences

This test of verbal memory is taken from the Neuropsychological Assessment of Dementia in Adults with Intellectual Disabilities (NAID) (Oliver *et al.* 1998). At baseline this test was administered to Cohort 2 only. Participants were asked to repeat 6 sentences after the researcher. The outcome measure was the number of words correctly remembered.

ACTB – virtual generated arena

The virtual generated arena is a measure of visuospatial short-term memory, taken from the ACTB (Edgin *et al.* 2010). This task was adapted from the C-G arena (Thomas *et al.* 2001) and is based on the Morris water maze from the animal literature (Morris 1984). The arena task was only administered to Cohort 2. This task required participants to learn and remember where a hidden carpet was in a virtual room, using visual cues around the room. The main outcome was the percentage of time searching in the correct quadrant in the final test trial when no carpet is present.

Tests of executive function

CANTAB – IED

The intra/extra dimensional set shift (IED) task is a measure of rule learning and set shifting from the CANTAB (CANTAB® 2016). Participants were required to learn rules about which was the 'correct' of two presented patterns. When a rule was established (6 consecutive correct answers) there was a rule change and participants were required to learn a new rule in the next stage. If a particular stage was not complete (i.e. that rule was not 'learnt') in a maximum of 50 trials the task terminated. The two main outcome measures were the number of stages completed (measure of set shifting) and the number of stage 1 errors (measure of rule learning). Completing stages 2-7 required an intra-dimensional shift, completing stages 8-9 required an extra-dimensional shift (stage 1 required rule learning only with no shift).

CANTAB – SRT

The simple reaction time (SRT) task from the CANTAB was originally proposed as a measure of attention (CANTAB® 2016), and was included in the ACTB as a measure of motor abilities (Edgin *et al.* 2010). Participants were required to press a button as soon as a white square appeared on the computer screen. There was an initial practice block of 24 trials, followed by two test blocks of 50 trials each. Outcome measures of interest were the standard deviation of the response time, which allows an estimate of consistency in response time and thus reflects attention levels during the task, the total number of correct responses, and mean response time.

Semantic verbal fluency

Verbal fluency is a measure of frontal function (Elfgren and Risberg 1998). Participants were asked to name as many animals as they could in 1 minute. The main outcome was the number of unique animals named (including age and sex variations). The number of animals repeated and the total number of repetitions are outcomes of future interest.

Tower of London

The Tower of London is intended to assess working memory and planning (Shallice 1982). Participants were required to move beads on a board to match presented configurations. We used a modified version of this task (Strydom *et al.* 2007), consisting of problems 1 to 5 from Krikorian *et al.* (1994) which can be completed in a minimum of 2-4 moves. Before commencing, the participant's ability to name the colour of each bead was tested to ensure they could distinguish between them (e.g. they were not red-green colour blind). The outcome measure was calculated from the number of trials completed, with 2 points for trials completed in the minimum number of moves and 1 point for trials completed with more moves.

ACTB – cats and frogs

The cats and frogs test measures rule learning and switching, inhibitory control, and working memory (Edgin *et al.* 2010) and is based on the Dots test (Davidson *et al.* 2006). We only administered this test to Cohort 2. Participants were required to learn two different rules in Stages 1 and 2 (the 'cat' and 'frog' rules respectively), and then combine them in Stage 3. For the 'cat' rule participants were required to press a button on the same side of the screen as the cat, for the 'frog' rule participants were required to press a button on the opposite side of the screen as the frog. Stage 1 contained 6 practice and 12 test trials, Stage 2 contained 4 practice and 12 test trials, and Stage 3 contained 33 test trials. We used the percentage of trials correctly completed for each stage as the outcome; Stages 1 and 2 rely on rule learning while Stage 3 relies on rule switching and inhibitory control. As piloting revealed some individuals showed response times that were too slow for the original version we amended the task to allow unlimited response times (Startin *et al.* unpublished observations). We also changed the cat colour to orange from white to contrast the green frog.

Tests of motor coordination

Finger-nose pointing

The finger-nose pointing test is a clinical measure of motor coordination (Desrosiers *et al.* 1995). Using the index finger on their dominant hand, participants alternatively pointed to the tip of their nose and a red circle with a 2cm diameter, 45cm away, as quickly as possible for 20 seconds. The outcome measure was the total number of times the participant pointed to the red circle.

NEPSY-II – visuomotor precision

This task measures hand-eye coordination, and is taken from the Developmental NEuroPSYchological Assessment-II (NEPSY-II) (Korkman *et al.* 2007). Participants were timed as they traced train, car, and motorbike tracks (divided into squares), with a time limit of 180s for each track. The number of errors was calculated for each track (defined as those squares where the line went outside the track, there was a broken line due to a pen lift, or squares not completed in the time limit). Error scores and times were used to determine an overall score firstly for the train and car tracks combined and secondly the car and motorbike tracks combined using provided tables.

ACTB – finger sequencing

The finger sequencing task is a measure of motor coordination. This task was adapted for the ACTB (Edgin *et al.* 2010) and administered to Cohort 2 only. Participants were required to tap a button as fast as possible using a variety of specified sequences, with a 10 second practice and 30 second test trial for each sequence. The total number of sequences completed was the main outcome used.

Informant questionnaires

Informants completed a series of questionnaires about the participant while the participant was administered the cognitive battery. Informants were usually relatives or paid carers. Missing items from the DLD, OMQ and BRIEF-A were imputed for up to 15% of items within each domain by checking and imputing the nearest integer to the mean value of completed scores within that domain by hand. All reported measures for these questionnaires use the total scores including imputed values where relevant.

Short ABS

The Short Adaptive Behavior Scale (short ABS) (Hatton *et al.* 2001), adapted from the Adaptive Behavior Scale – Residential and Community (Part I) (Nihira *et al.* 1993), recorded participants' everyday adaptive abilities.

DLD

The Dementia for Learning Disabilities (DLD) questionnaire is a measure of behaviours associated with cognitive decline in people with ID over the last two months (Evenhuis 1996).

OMQ

The Observer Memory Questionnaire (OMQ) is an informant reported questionnaire relating to individuals' memory abilities over the last two months (O'Shea 1996).

BRIEF-A

The Behavior Rating Inventory of Executive Function – Adult version (BRIEF-A) (Roth *et al.* 2005) provides scores for informant reported problems with behaviours relating to executive functioning over the last month.

Statistical analysis

The results presented here are limited to cross-sectional analyses of cognitive task data and related informant questionnaires. All statistical analyses were performed using SPSS version 22. We determined the number of individuals who completed each task, and for each outcome measure of interest calculated the mean, standard deviation and range of scores. As many variables deviated from normality as assessed using the Shapiro-Wilk test, with alpha set to $p < 0.01$ to account for multiple comparisons, we also calculated medians and interquartile ranges. We determined the percentage of individuals at floor and ceiling level for each outcome of those who were able to complete the task (i.e. the number of individuals scoring the lowest and highest possible scores respectively). We compared responses between males and females in Cohort 2 using Student's t-tests or Mann-Whitney U tests as appropriate. Correlation analyses were performed for Cohort 2 using Pearson's correlation or Spearman's rho as appropriate to assess concurrent validity and to determine the relationships between selected test scores; for these alpha was set to $p < 0.01$ due to multiple comparisons. Absolute values of correlation coefficients of 0.70 and above were considered strong, between 0.50 and 0.69 were considered moderate, and between 0.30 and 0.49 were considered weak.

Results

Task completion and score distributions

Cohort 1: adults aged 36 years and over without dementia

Demographic information of 130 adults aged 36+ years without a clinical diagnosis of dementia is shown in Table 1. Nine (6.9%) participants were unable to undertake any tasks (one of whom did not understand English) and a further 12 (9.2%) participants did not pass the vision and hearing tests. All data relating to cognitive task completion and performance for this group are presented for 109 adults in Table 2, and data from informant questionnaires are shown in Table 3.

Completion rates for each cognitive task in our battery were acceptable, approximately 90% for all non-computer tasks and 80% for computer tests. For those who completed the tasks many outcomes showed fewer than 10% of participants at floor and fewer than 20% of participants at ceiling. As anticipated, when converting KBIT-2 raw scores to IQ we found a high number of adults at floor, with 70 (66.7%) adults at floor for verbal IQ and 41 (39.4%) adults at floor for non-verbal IQ. The majority of outcomes from the informant questionnaires showed low floor and ceiling effects.

Cohort 1: adults aged 36 years and over with dementia

Information about the demographics of 51 individuals with clinically diagnosed dementia is shown in Table 1. Of these, 22 had a diagnosis of AD, 1 a diagnosis of vascular dementia, 1 a diagnosis of dementia with Lewy bodies, and 27 had dementia of unspecified type. The mean age of dementia diagnosis was 51.70 years (SD 6.80, range 35-65 years), with a mean time since diagnosis of 2.46 years (SD 2.42, range 0-11 years). Of the adults in this group, 15 (29.4%) were unable to undertake any cognitive task with a further 9 (17.6%) failing the vision or hearing task. All data relating to cognitive task completion and performance for this group are presented for 27 individuals in Table 4, with data from informant questionnaires in Table 5.

Completion rates for adults with dementia were lower than for those without dementia. Almost all tasks showed completion rates above 65%. For those able to complete the task the majority of outcomes showed fewer than 25% of individuals at floor and fewer than 15% of participants at ceiling. Again, we found high floor effects when converting KBIT-2 raw scores to IQ, with 21 (84.0%) adults at floor for verbal IQ and 15 (62.5%) adults at floor for non-verbal IQ. From the informant questionnaires, domains showed minimal floor and ceiling effects.

Cohort 2: adults aged 16-35 years

Analyses were conducted for 124 adults aged 16-35 years. Demographic information is shown in Table 1. Of these, three (2.4%) did not pass the vision test, and so results relating to cognitive task performance for this group are presented for 121 individuals in Table 6 with data from informant questionnaires in Table 7. We found high completion rates across the tasks in the battery, with the majority above 85% and many of the lower completion rates for some of the computer tasks being due to technical problems. For those who completed the tasks there were low floor effects, with many outcomes having fewer than 5% of participants at floor. Some outcomes however showed relatively high ceiling effects, though many were below 35%. When converting raw KBIT-2 scores to IQ we again found high floor effects, with 61 (50.8%) adults at floor for verbal IQ and 41 (33.9%) adults at floor for non-verbal IQ. The majority of domains from the informant questionnaires showed low floor and ceiling effects, although ceiling effects were found in over 20% of individuals for domains in the short ABS and DLD.

Comparing scores for males and females in Cohort 2

There was no significant difference in age between males and females ($t(122)=-0.854$, $p=0.395$, male M 24.80 SD 5.79, females M 25.65 SD 5.29, 95% CI (-2.82, 1.12)). Females showed significantly better performance on the verbal subtests of the KBIT-2 ($t(109.5)=-2.15$, $p=0.034$, 95% CI (-12.40, -0.50)). For the informant questionnaires females showed better cognitive abilities as assessed by the DLD cognitive domain ($p=0.041$). There were no other significant differences in performance between males and females (all $p>0.05$; see Table 8 and Table 9). Within Cohort 2 there were no significant correlations with age for any cognitive test outcomes or informant questionnaire scores (all $p>0.05$; see Table 10 and Table 11).

Correlations between outcome scores for Cohort 2

The majority of cognitive test outcomes showed significant correlations with all other outcomes in the battery ($p<0.01$), with the exception of the computer generated arena which showed no significant correlations at the $p<0.01$ level (Table 10). All outcomes from the informant questionnaires showed significant correlations with each other (see Table 11). Due to a high number of adults aged 16-35 scoring at or close to ceiling in the DLD domains these scores were not included in correlational analyses.

To better investigate the relationships between test outcomes we considered the absolute values of correlation coefficients.

Moderate and strong correlations revealed four clusters of test outcomes within our cognitive data. One cluster contained PAL first trial memory score and object memory immediate score ($r=0.522$), suggesting this is a visuospatial memory cluster. Another contained SRT mean latency and latency standard deviation, finger-nose pointing and finger sequencing ($0.539<r<0.628$), suggesting this is a motor coordination cluster. The next contained memory for sentences and verbal fluency ($r=0.593$). These two tasks also correlated highly with KBIT-2 verbal and non-verbal scores ($0.503<r<0.827$), in particular the former, suggesting this represents a language cluster. The final cluster contained outcomes that were not all necessarily related to each other but were related to at least two other outcomes in the cluster; this consisted of PAL first trial memory score, SRT mean latency and latency standard deviation, Tower of

London, finger-nose pointing and NEPSY-II visuomotor precision car and motorbike ($0.271 < r < 0.614$). Again, most of this cluster correlated with KBIT-2 verbal and non-verbal scores ($0.380 < r < 0.636$). This cluster may be related to processing speed and sustained attention. Finally, the cats and frogs Stage 3 score also correlated highly with KBIT-2 verbal and non-verbal scores ($r=0.568$ and $r=0.541$ respectively), suggesting performance on this task is highly related to general abilities.

Within the informant questionnaire outcomes the best correlations were between subscales related to complex adaptive functioning such as personal-social responsibility and higher cognitive functions (Short ABS Personal-social responsibility and OMQ $r=-0.631$, Short ABS Personal-social responsibility and BRIEF-A Metacognition index $r=-0.731$).

Discussion

Here we describe a cognitive test battery to provide detailed assessment of cognitive abilities in individuals with DS, along with data for test completion and outcomes. We deliberately assessed individuals with a wide range of ages and ID severities and those with and without a clinical diagnosis of dementia, in order to provide cognitive test data that is representative of the adult population with DS. Results from individuals without dementia suggest high completion rates across the tasks. Computer-based tasks had lower completion rates, in some cases (up to 27.3%) due to technical issues. Completion rates for those with dementia were lower, with approximately half of individuals unable to undertake any task. Our outcome measures for each task and informant measure showed a range of scores, with many showing low floor and ceiling effects. Non-verbal age-adjusted IQ scores had lower floor effects than verbal IQ scores for all groups.

Females aged 16-35 years performed better than males on general verbal abilities, and also showed better cognitive abilities as assessed by the DLD cognitive domain. We identified clusters of cognitive test scores within our battery relating to visuospatial memory, motor coordination, language abilities, and processing speed / sustained attention.

Our results show a wide range of individuals' cognitive abilities, and suggest our battery is suitable for a wide range of adults with DS. Our future studies will use our baseline results presented here to investigate cognitive abilities and changes in cognitive abilities associated with ageing and dementia. Individual differences in the dementia phenotype and cognitive profiles of people with DS emphasises the importance of studying factors contributing towards these variations (Karmiloff-Smith *et al.* 2016). We will also investigate factors including genetic, medical and socioeconomic variations that may be associated with these abilities. We hope our results will help identify risk and protective factors for the development of dementia in people with DS, and factors relating to baseline cognitive abilities. This will aid identifying relevant potential mechanisms and predictive phenotypes, and may help to inform interventions that can influence developmental trajectories.

Final test and outcome selection

Many of the tests within our battery show a range of scores with low floor and ceiling effects and high validity, as determined by exploring relationships between outcomes in Cohort 2. However, several tests within our battery may have limited use based on our study aims. Firstly, the CAMCOG incidental memory test may not be useful, with high floor effects for the recall score for all groups. Future longitudinal studies will determine if this is a useful test to assess cognitive decline within individuals. Secondly, a previous pilot study suggested the virtual generated arena is not useful in older adults (Sinai and Strydom unpublished observations), and our current analyses showed that for younger adults the test scores showed limited correlations with other task measures. Further, both the mean and median times spent in the correct quadrant were approximately 25%, and as individuals should spend 25% of their time in the correct quadrant by chance alone this suggests this measure is not useful.

As expected, when converting raw scores on the KBIT-2 to age-dependent IQ scores we found high floor effects across all participant groups. IQ score floor effects were lower for non-verbal IQ than verbal IQ in all our groups. Age-dependent non-verbal IQ scores may therefore be more useful than verbal IQ scores for future studies, and also offer an advantage if comparing individuals or studies across language groups.

The ideal test and outcome measure to use in neuropsychological research depends upon the cognitive ability of interest, the specific research question and population assessed, in addition to floor / ceiling effects and the spread of results observed. Within different age cohorts and for our different research questions different tests and outcome measures will therefore be useful, in particular as score ranges and floor and ceiling effects varied across groups (e.g. to assess cognitive decline then outcomes with low floor effects prior to the onset of decline are essential). For several cognitive tasks within our battery, in particular the CANTAB tasks, there are multiple outcome measures, and we have identified those outcomes that will be most useful in our future studies (see Box 1).

A high proportion of individuals with dementia were unable to complete any cognitive tests. For those able to undertake cognitive tasks completion rates were generally higher for table-top tasks compared to computer tasks. This suggests the use of some longer computer tasks may not be suitable for an older population at risk for dementia, and instead may need to be replaced with traditional table-top tasks and

informant questionnaires. We also noted that in many adults with dementia and in some adults aged 36+ years without dementia attention levels appeared to negatively affect task performance. A similar observation was made by Sinai *et al.* (2016), and future test batteries should account for this.

Finally, during data collection we found some questions within two of the informant questionnaires used, the BRIEF-A and OMQ, were often unsuitable for older adults and those with more severe IDs. As a result, we developed a new informant questionnaire, the Cognitive Scale for Down Syndrome (CS-DS), to assess cognitive abilities in people with DS, focusing on executive function, memory and language abilities. This questionnaire showed high reliability and validity (Startin *et al.* 2016).

Validity of the test battery

The majority of cognitive test scores correlated well with all other cognitive test scores in adults aged 16-35. It has previously been proposed that cognitive measures are more highly correlated in those with lower compared to higher IQs (Detterman and Daniel 1989). The high correlations between test scores and KBIT-2 raw scores indicate that higher general abilities are related to better individual task performance, and it has similarly been suggested the high variability in neurocognitive task performance in people with DS is due to variability in IQ (de Sola *et al.* 2015). Further, de Sola *et al.* (2015) and Liogier d'Ardhuy *et al.* (2015) found better task performance in individuals with higher IQs.

To determine clusters of related cognitive outcomes in adults aged 16-35 before the onset of cognitive decline we examined correlational coefficients of 0.50 and above. We identified the presence of clusters relating to visuospatial memory, motor coordination, language abilities, and sustained attention / processing speed. These results suggest the presence of related cognitive abilities in this population that could inform further development of outcome measures.

Effect of sex on task performance

We found females scored higher for KBIT-2 verbal scores and for informant report for the DLD cognitive domain than males in adults aged 16-35 years. Previous studies have also reported higher linguistic abilities in females compared to males (de Sola *et al.* 2015, Liogier d'Ardhuy *et al.* 2015), in addition to better performance on tasks of memory, executive function and attention (including the PAL and SRT) (de Sola *et al.* 2015) and higher functional abilities (Lund 1988, Maatta *et al.* 2006). The effect of gender on cognitive and functional abilities in DS requires further study.

Possible effect of cognitive decline and ageing on task performance

We found no significant correlations with age and cognitive test outcomes or informant questionnaire scores in adults aged 16-35. Performance was however generally poorer in adults aged 36+ compared to those aged 16-35. Our future analyses will focus on the impact of cognitive decline and ageing on abilities in individuals with DS.

Previous studies have confirmed poorer performance on many of the cognitive tasks within our battery for adults with cognitive decline or dementia compared to those with no decline (Adams and Oliver 2010, Ball *et al.* 2008, Oliver *et al.* 2005, Sinai *et al.* 2016). Previous studies have also found poorer performance associated with ageing in DS for the PAL (Crayton *et al.* 1998, Oliver *et al.* 2005) and Tower of London (Ghezzi *et al.* 2014). These results suggest our battery should be sensitive to the presence of dementia and many of our tasks may be useful for predicting and tracking cognitive decline. Cognitive abilities and changes in these individuals over the course of our longitudinal study will be of particular interest when determining the effects of age-related and dementia-related changes in cognition.

Strengths and limitations

A major strength of our study and analyses is the large sample size, including a wide variety of ages and ID severities, and both those with and without a clinical diagnosis of dementia. We recruited individuals from a variety of settings, including volunteers and local ID clinical teams, suggesting our sample should be representative of individuals with DS in the UK.

Our results suggest the majority of our tasks have high completion rates for adults who do not have a diagnosis of dementia, with test scores showing a wide range and select outcomes showing low floor and ceiling effects. The battery will therefore be largely suitable for further analyses to assess cognitive decline, dementia, ageing, and baseline cognitive abilities in adults with DS.

For adults with a diagnosis of dementia completion rates were much lower however, although this population will always be difficult to assess with psychometric tests. For adults unable to complete any of the tasks in the battery informant ratings of abilities are invaluable, although further work is needed to determine the relationships between cognitive test scores and informant measure outcomes. A further limitation lies with the use of KBIT-2 IQ scores, which showed a high number of individuals at floor level, similar to other IQ tests in this population. For this reason we chose to use raw scores as the main outcome for the KBIT-2.

Conclusion

We report a cognitive battery and related informant measures to assess general abilities, memory, executive function, and motor coordination abilities in individuals with DS. We assessed participants with a range of ages and abilities, and our results suggest the battery is suitable for the majority of adults with DS. Many test outcomes showed a range of scores with low floor and ceiling effects. This battery will be used in our future studies to assess factors influencing individual differences in cognitive decline, dementia, ageing, and baseline cognitive abilities in adults with DS.

Data availability

Raw scores for KBIT-2 and total scores for informant questionnaires can be found for each cohort with the online version of this article.

Author contributions

AS conceived the adult cohort study in conjunction with LonDownS principal investigators; TA managed NHS site collaborations; CMS, SH, RH, AD, ER and NA performed data collection; CMS and AS designed the data analysis and analysed the data; CMS, SH, RH, TA and AS wrote the paper.

Competing interests

AS has acted as an investigator for clinical trials sponsored by Roche Pharmaceuticals and consulted for Ono pharmaceuticals. He has been an adviser to the UK Down Syndrome Association and is an advisory board member of the LuMind Foundation (USA). No other authors have any competing interests to declare.

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Supplementary material

S1. Summary table of assessments for general abilities, memory, executive function, and motor coordination, with outcomes of interest. All assessments are listed, in addition to a brief description of the test and ability assessed, and outcome measures and the possible range of scores.

S2. Assessment schedule for cognitive test battery. The counter-balanced order of tests used is given for participants in the two cohorts.

Tables

	Adults aged 36+ without dementia	Adults aged 36+ with dementia	Adults aged 16-35
Number	130	51	124
Age (mean±SD (range))	47.77±7.01 (36-71)	54.20±6.95 (38-67)	25.24±5.53 (16-35)
Sex	74 males, 56 females	22 males, 29 females	59 males, 65 females
ID severity (carer report)	55 mild, 53 moderate, 22 severe	16 mild, 22 moderate, 8 severe, 5 unknown (NB pre-dementia)	48 mild, 63 moderate, 13 severe
Ethnicity	112 white, 4 Asian, 10 African, 3 mixed, 1 other	48 white, 2 Asian, 1 African	101 white, 6 Asian, 7 African, 7 mixed, 3 other

Table 1. Participant demographics across the groups.

Test	Number completed	Reasons for non-completion	Outcome measure	Mean ± SD	Median (IQR)	Range	Number at floor	Number at ceiling
KBIT-2	105 (96.3%) verbal, 104 (95.4%) non-verbal	5 unable to complete	Verbal raw score	30.55 ± 17.47	28.00 (24.00)	2 - 80	0 (0.0%)	0 (0.0%)
			Performance raw score ^a	12.55 ± 6.57	14.00 (7.00)	0 - 32	7 (6.7%)	0 (0.0%)
CANTAB – PAL	91 (83.5%)	10 refused 8 unable to complete	First trial memory score ^a	7.00 ± 5.86	6.00 (11.00)	0 - 21	15 (16.5%)	0 (0.0%)
			Levels completed ^a	4.98 ± 2.65	5.00 (6.00)	0 - 8	5 (5.5%)	23 (25.3%)
CAMCOG – delayed incidental memory	100 (91.7%)	7 refused 2 unable to complete	Object naming ^a	5.65 ± 0.70	6.00 (1.00)	3 - 6	0 (0.0%)	75 (75.0%)
			Object recall ^a	0.52 ± 1.05	0.00 (1.00)	0 - 6	72 (72.0%)	1 (1.0%)
			Object recognition ^a	3.47 ± 1.85	4.00 (3.00)	0 - 6	6 (6.0%)	18 (18.0%)
CAMCOG – orientation	100 (91.7%)	6 refused 3 unable to complete	Total score ^a	8.87 ± 3.56	10.50 (6.00)	0 - 12	1 (1.0%)	40 (40.0%)
Delayed object memory	97 (89.0%)	6 refused 4 unable to complete 2 technical problems	Immediate memory ^a	9.09 ± 3.17	10.00 (5.00)	0 - 14	2 (2.1%)	4 (4.1%)
			Delayed memory ^a	5.07 ± 1.80	5.00 (2.00)	0 - 7	3 (3.1%)	22 (22.7%)
CANTAB – IED	89 (81.7%)	14 refused 5 unable to complete 1 technical problems	Errors in stage 1 ^{a b}	6.29 ± 9.17	2.00 (5.50)	0 - 33	0 (0.0%)	11 (12.4%) ^c
			Levels completed ^a	5.83 ± 3.07	7.00 (3.00)	0 - 9	13 (14.6%)	17 (19.1%)
CANTAB – SRT	84 (77.1%)	13 refused 7 unable to complete 5 technical problems	Total correct ^a	87.07 ± 17.29	94.00 (17.25)	25 - 100	0 (0.0%)	13 (15.5%)
			Mean latency (ms) ^{a b}	950.37 ± 480.55	853.78 (631.36)	311.33 - 2241.61	N/A	N/A
			Latency	445.17	426.63	45.32 -	N/A	N/A

			standard deviation (ms) ^b	± 216.29	(349.09)	980.98		
CAMCOG – verbal fluency	101 (92.7%)	6 refused 2 unable to complete	Total animals named ^a	8.40 ± 5.86	8.00 (8.00)	0 - 27	6 (5.9%)	N/A
Tower of London	97 (89.0%)	5 refused 6 unable to complete 1 technical problems	Total score ^a	6.37 ± 3.23	8.00 (5.00)	0 - 10	8 (8.2%)	17 (17.5%)
Finger-nose pointing	98 (89.9%)	9 refused 2 unable to complete	Total completed ^a	8.49 ± 4.83	8.00 (6.00)	0 - 23	2 (2.0%)	N/A
NEPSY-II – visuomotor precision	97 (89.0%) train and car, 96 (88.1%) car and motorbike	10 refused 2 unable to complete 1 technical problems	Train and car ^a	13.52 ± 5.88	15.00 (8.00)	1 - 23	0 (0.0%)	0 (0.0%)
			Car and motorbike ^a	11.45 ± 8.72	9.00 (15.00)	0 - 32	3 (3.1%)	0 (0.0%)

Table 2. Task completion rates and summary of results for main outcome measures for adults aged 36+ without dementia. ^a Significantly deviated from normality using Shapiro-Wilk test (P<0.010), ^b lower values indicate better performance, ^c 0 errors is at ceiling.

Questionnaire	Outcome measure	Number completed	Mean ± SD	Median (IQR)	Range	Number at floor	Number at ceiling
Short ABS	Total score	112 (86.2%)	71.89 ± 23.39	75.00 (38.50)	14 - 111	0 (0.0%)	0 (0.0%)
	Personal self-sufficiency ^a	117 (90.0%)	26.74 ± 6.07	29.00 (6.00)	0 - 33	1 (0.9%)	14 (12.0%)
	Community self-sufficiency	115 (88.5%)	24.57 ± 12.06	24.00 (17.00)	0 - 47	1 (0.9%)	0 (0.0%)
	Personal-social responsibility ^a	116 (89.2%)	20.78 ± 6.97	21.00 (10.75)	3 - 32	0 (0.0%)	1 (0.9%)
DLD^b	Sum of cognitive score ^a	110 (84.6%)	12.23 ± 10.74	9.00 (16.50)	0 - 38	0 (0.0%)	12 (10.9%)
	Sum of social scores ^a	113 (86.9%)	11.58 ± 7.75	11.00 (10.00)	0 - 36	0 (0.0%)	6 (5.3%)
OMQ^b	Total score	111 (85.4%)	82.50 ± 18.85	83.00 (26.00)	35 - 125	0 (0.0%)	0 (0.0%)
BRIEF-A^b	Total score	100 (76.9%)	122.11 ± 24.11	122.00 (37.50)	74 - 175	0 (0.0%)	0 (0.0%)
	Behavioural regulation index	117 (90.0%)	52.02 ± 11.21	51.00 (16.00)	30 - 80	0 (0.0%)	2 (1.7%)
	Metacognition index	101 (77.7%)	70.91 ± 14.71	72.00 (22.50)	43 - 100	0 (0.0%)	0 (0.0%)

Table 3. Summary of results from informant questionnaires for adults aged 36+ without dementia. ^a Significantly deviated from normality using Shapiro-Wilk test (P<0.010), ^b higher scores indicate poorer abilities.

Test	Number completed	Reasons for non-completion	Outcome measure	Mean ± SD	Median (IQR)	Range	Number at floor	Number at ceiling
KBIT-2	25 (92.6%) verbal, 24 (88.9%) non-verbal	3 unable to complete	Verbal raw score	18.68 ± 13.77	17.00 (24.00)	1 - 51	0 (0.0%)	0 (0.0%)
			Performance raw score	8.29 ± 6.45	8.00 (12.00)	0 - 19	4 (16.7%)	0 (0.0%)
CANTAB – PAL	20 (74.1%)	2 refused 5 unable to complete	First trial memory score ^a	1.70 ± 2.58	0.50 (2.75)	0 - 9	10 (50.0%)	0 (0.0%)
			Levels completed	2.40 ± 2.09	2.00 (4.50)	0 - 6	5 (25.0%)	0 (0.0%)
CAMCOG – delayed incidental memory	25 (92.6%)	2 unable to complete	Object naming ^a	5.40 ± 0.87	6.00 (2.00)	4 - 6	0 (0.0%)	16 (64.0%)

			Object recall ^a	0.16 ± 0.47	0.00 (0.00)	0 - 2	22 (88.0%)	0 (0.0%)
			Object recognition	2.84 ± 1.70	2.00 (2.00)	0 - 6	1 (4.0%)	3 (12.0%)
CAMCOG – orientation	23 (85.2%)	3 unable to complete 1 technical problems	Total score	5.65 ± 3.92	5.00 (7.00)	0 - 12	2 (8.7%)	2 (8.7%)
Delayed object memory	21 (77.8%)	3 unable to complete 3 technical problems	Immediate memory ^a	4.62 ± 4.12	3.00 (8.00)	0 - 11	5 (23.8%)	0 (0.0%)
			Delayed memory	2.67 ± 2.22	2.00 (5.00)	0 - 7	5 (23.8%)	1 (4.8%)
CANTAB – IED	20 (74.1%)	1 refused 6 unable to complete	Errors in stage 1 ^{a,b}	13.70 ± 12.91	7.00 (23.75)	0 - 39	0 (0.0%)	3 ^c (15.0%)
			Levels completed ^a	3.30 ± 3.39	1.50 (7.00)	0 - 8	8 (40.0%)	0 (0.0%)
CANTAB – SRT	17 (63.0%)	3 refused 7 unable to complete	Total correct	73.88 ± 18.83	72.00 (36.00)	41 - 99	0 (0.0%)	0 (0.0%)
			Mean latency (ms) ^b	1293.65 ± 488.29	1160.93 (893.95)	588.00 - 2153.17	N/A	N/A
			Latency standard deviation (ms) ^b	574.87 ± 166.43	609.07 (252.62)	219.57 - 815.67	N/A	N/A
CAMCOG – verbal fluency	25 (92.6%)	2 unable to complete	Total animals named ^a	5.00 ± 4.51	5.00 (7.00)	0 - 19	4 (16.0%)	N/A
Tower of London	16 (59.3%)	11 unable to complete	Total score	4.88 ± 3.79	5.50 (8.00)	0 - 10	3 (18.8%)	3 (18.8%)
Finger-nose pointing	23 (85.2%)	2 refused 2 unable to complete	Total completed ^a	5.61 ± 5.09	3.00 (9.00)	0 - 15	2 (8.7%)	N/A
NEPSY-II – visuomotor precision	19 (70.4%) train and car, 18 (66.7%) car and motorbike	1 refused 8 unable to complete	Train and car	11.00 ± 7.57	11.00 (15.00)	0 - 21	1 (5.3%)	0 (0.0%)
			Car and motorbike	7.67 ± 7.90	5.00 (13.00)	0 - 24	4 (22.2%)	0 (0.0%)

Table 4. Task completion rates and summary of results for main outcome measures for adults aged 36+ with dementia^a Significantly deviated from normality using Shapiro-Wilk test (P<0.010),^b lower values indicate better performance, ^c0 errors is at ceiling.

Questionnaire	Outcome measure	Number completed	Mean ± SD	Median (IQR)	Range	Number at floor	Number at ceiling
Short ABS	Total score	43 (84.3%)	42.23 ± 24.51	38.00 (42.00)	3 - 92	0 (0.0%)	0 (0.0%)
	Personal self-sufficiency	43 (84.3%)	17.02 ± 9.70	17.00 (18.00)	0 - 33	1 (2.3%)	1 (2.3%)
	Community self-sufficiency ^a	43 (84.3%)	11.98 ± 9.11	10.00 (15.00)	0 - 31	1 (2.3%)	0 (0.0%)
	Personal-social responsibility	43 (84.3%)	13.23 ± 7.32	13.00 (11.00)	1 - 28	0 (0.0%)	0 (0.0%)
DLD^b	Sum of cognitive score	42 (82.4%)	27.69 ± 10.53	29.00 (13.25)	3 - 44	1 (2.4%)	0 (0.0%)
	Sum of social scores	42 (82.4%)	23.93 ± 12.01	25.00 (22.00)	1 - 50	0 (0.0%)	0 (0.0%)
OMQ^b	Total score	37 (72.5%)	117.16 ± 13.82	119.00 (13.50)	78 - 142	0 (0.0%)	0 (0.0%)
BRIEF-A^b	Total score	33 (64.7%)	145.36 ± 31.54	149.00 (40.50)	77 - 199	0 (0.0%)	0 (0.0%)
	Behavioural regulation index	37 (72.5%)	57.22 ± 14.71	54.00 (21.00)	32 - 84	0 (0.0%)	0 (0.0%)

	Metacognition index	33 (64.7%)	88.24 ± 19.53	94.00 (30.00)	43 - 118	0 (0.0%)	0 (0.0%)
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Table 5. Summary of results from informant questionnaires for adults aged 36+ with dementia. ^a

Significantly deviated from normality using Shapiro-Wilk test ($P < 0.010$), ^b higher scores indicate poorer abilities.

Test	Number completed	Reasons for non-completion	Outcome measure	Mean ± SD	Median (IQR)	Range	Number at floor	Number at ceiling
KBIT-2	120 (99.2%) verbal, 121 (100.0%) non-verbal	1 unable to complete	Verbal raw score	35.03 ± 16.77	35.00 (23.00)	2 - 82	0 (0.0%)	0 (0.0%)
			Performance raw score ^a	14.98 ± 6.90	16.00 (7.00)	0 - 32	5 (4.1%)	0 (0.0%)
CANTAB – PAL	108 (89.3%)	5 refused 7 unable to complete 1 technical problems	First trial memory score ^a	10.22 ± 5.66	11.00 (7.75)	0 - 20	10 (9.3%)	0 (0.0%)
			Levels completed ^a	6.29 ± 2.50	8.00 (2.00)	0 - 8	4 (3.7%)	56 (51.9%)
CAMCOG – delayed incidental memory	117 (96.7%)	1 refused 2 unable to complete 1 technical problems	Object naming ^a	5.74 ± 0.68	6.00 (0.00)	2 - 6	0 (0.0%)	98 (83.8%)
			Object recall ^a	1.19 ± 1.42	1.00 (2.00)	0 - 6	53 (45.3%)	1 (0.9%)
			Object recognition ^a	4.30 ± 1.59	5.00 (3.00)	0 - 6	2 (1.7%)	34 (29.1%)
CAMCOG – orientation	113 (93.4%)	1 refused 4 unable to complete 3 technical problems	Total score ^a	9.65 ± 3.45	12.00 (4.00)	1 - 12	0 (0.0%)	65 (57.5%)
Delayed object memory	109 (90.1%)	2 refused 3 unable to complete 7 technical problems	Immediate memory ^a	10.35 ± 2.83	11.00 (3.00)	0 - 14	2 (1.8%)	3 (2.8%)
			Delayed memory ^a	5.84 ± 1.42	6.00 (2.00)	0 - 7	1 (0.9%)	43 (39.4%)
Memory for sentences	106 (87.6%)	2 refused 10 unable to complete 3 technical problems	Total words remembered ^a	30.53 ± 13.68	33.50 (23.00)	3 - 49	0 (0.0%)	3 (2.8%)
ACTB – virtual generated arena	73 (60.3%)	4 refused 11 unable to complete 33 technical problems	Percentage of time spent in correct quadrant ^a	26.52 ± 19.88	22.36 (21.04)	0.00 - 86.79	8 (11.0%)	0 (0.0%)
CANTAB – IED	109 (90.1%)	2 refused 6 unable to complete 4 technical problems	Errors in stage 1 ^{a,b}	4.19 ± 7.16	2.00 (3.00)	0 - 33	0 (0.0%)	19 (17.4%) _c
			Levels completed ^a	6.57 ± 2.54	7.00 (1.00)	0 - 9	9 (8.3%)	22 (20.2%)
CANTAB – SRT	105 (86.8%)	3 refused 6 unable to complete 7 technical problems	Total correct ^a	92.82 ± 13.30	98.00 (8.00)	13 - 100	0 (0.0%)	35 (33.3%)
			Mean latency (ms) ^{a,b}	692.48 ± 442.59	553.77 (462.81)	273.37 - 2500.61	N/A	N/A

			Latency standard deviation (ms) ^{a b}	315.93 ± 208.43	274.23 (295.32)	32.94 - 950.49	N/A	N/A
CAMCOG – verbal fluency	114 (94.2%)	1 refused 5 unable to complete 1 technical problems	Total animals named	10.93 ± 5.84	10.50 (10.00)	0 - 24	3 (2.6%)	N/A
Tower of London	112 (92.6%)	3 unable to complete 6 technical problems	Total score ^a	7.45 ± 2.90	8.00 (2.00)	0 - 10	6 (5.4%)	26 (23.2%)
ACTB – cats and frogs	86 (71.1%)	4 refused 3 unable to complete 28 technical problems	Stage 1 (cat rule alone) percentage correct ^a	90.31 ± 18.57	100.00 (9.32)	33.33 - 100.00	0 (0.0%)	59 (68.6%)
			Stage 2 (frog rule alone) percentage correct ^a	79.83 ± 27.12	95.83 (33.33)	0.00 – 100.00	2 (2.3%)	43 (50.0%)
			Stage 3 (combined rules) percentage correct ^a	66.96 ± 21.64	56.16 (44.02)	33.33 - 100.00	0 (0.0%)	13 (15.1%)
Finger-nose pointing	116 (95.9%)	3 refused 2 technical problems	Total completed	11.01 ± 5.19	10.50 (8.00)	0 - 24	1 (0.9%)	N/A
NEPSY-II – visuomotor precision	118 (97.5%)	3 technical problems	Train and car ^a	15.90 ± 5.26	18.00 (5.00)	2 - 23	0 (0.0%)	0 (0.0%)
			Car and motorbike ^a	17.00 ± 9.61	18.00 (16.00)	0 - 40	1 (0.8%)	0 (0.0%)
ACTB – finger sequencing	83 (68.6%)	3 refused 10 unable to complete 25 technical problems	Total complete sequences	231.42 ± 62.36	241.00 (75.00)	30 - 369	0 (0.0%)	N/A

Table 6. Task completion rates and summary of results for main outcome measures for adults aged 16-35.

^a Significantly deviated from normality using Shapiro-Wilk test (P<0.010), ^b lower values indicate better performance, ^c 0 errors is at ceiling.

Questionnaire	Outcome measure	Number completed	Mean ± SD	Median (IQR)	Range	Number at floor	Number at ceiling
Short ABS	Total score ^a	118 (95.2%)	79.03 ± 19.73	84.00 (28.50)	28 - 112	0 (0.0%)	0 (0.0%)
	Personal self-sufficiency ^a	119 (96.0%)	28.91 ± 4.55	30.00 (6.00)	14 - 33	0 (0.0%)	31 (26.1%)
	Community self-sufficiency	119 (96.0%)	27.74 ± 10.36	29.00 (15.00)	4 - 47	0 (0.0%)	0 (0.0%)
	Personal-social responsibility ^a	119 (96.0%)	22.53 ± 6.49	23.00 (10.00)	7 - 32	0 (0.0%)	5 (4.2%)
DLD^b	Sum of cognitive score ^a	114 (91.9%)	7.57 ± 8.40	4.00 (11.00)	0 - 39	0 (0.0%)	23 (20.2%)
	Sum of social scores ^a	118 (95.2%)	9.32 ± 6.85	8.50 (8.00)	0 - 31	0 (0.0%)	9 (7.6%)
OMQ^b	Total score	119 (96.0%)	74.82 ± 18.43	75.00 (23.00)	33 - 120	0 (0.0%)	0 (0.0%)
BRIEF-A^b	Total score	113 (91.1%)	121.03 ± 26.27	121.00 (31.00)	71 - 191	0 (0.0%)	0 (0.0%)
	Behavioural regulation index ^a	117 (94.4%)	50.75 ± 12.32	49.00 (17.00)	31 - 82	0 (0.0%)	0 (0.0%)
	Metacognition index	113 (91.1%)	70.55 ± 16.71	70.00 (18.00)	40 - 116	0 (0.0%)	2 (1.8%)

Table 7. Summary of results from informant questionnaires for adults aged 16-35. ^a Significantly deviated from normality using Shapiro-Wilk test (P<0.010), ^b higher scores indicate poorer abilities.

	Mean ± SD	Median (IQR)			p
	Males	Females	Males	Females	
KBIT-2 verbal score ^a	31.75 ± 13.68	38.20 ± 18.87	32.00 (16.00)	38.00 (28.00)	0.034
KBIT-2 non-verbal score	14.97 ± 6.90	15.00 ± 6.95	16.00 (7.00)	16.00 (7.00)	0.845
PAL first trial memory score	10.04 ± 5.17	10.39 ± 6.12	10.00 (7.00)	12.50 (11.00)	0.444
PAL levels completed	6.35 ± 2.37	6.23 ± 2.63	7.50 (2.00)	8.00 (3.50)	0.806
CAMCOG object naming	5.75 ± 0.61	5.74 ± 0.75	6.00 (0.00)	6.00 (0.00)	0.702
CAMCOG object recall	1.11 ± 1.34	1.26 ± 1.49	1.00 (2.00)	1.00 (2.00)	0.657
CAMCOG object recognition	4.07 ± 1.72	4.51 ± 1.45	4.50 (4.00)	5.00 (2.00)	0.207
CAMCOG orientation	9.18 ± 3.59	10.10 ± 3.29	11.00 (6.00)	12.00 (3.00)	0.086
Object memory immediate	10.30 ± 2.48	10.39 ± 3.15	11.00 (3.00)	11.00 (2.00)	0.367
Object memory delayed	5.91 ± 1.15	5.79 ± 1.65	6.00 (2.00)	6.00 (2.00)	0.664
Memory for sentences	29.16 ± 13.33	31.80 ± 14.00	33.00 (22.00)	34.00 (24.00)	0.267
IED errors stage 1	3.62 ± 6.12	4.72 ± 8.01	1.50 (3.00)	2.00 (3.00)	0.874
IED levels complete	6.88 ± 2.28	6.28 ± 2.74	7.00 (1.00)	7.00 (0.50)	0.212
SRT total correct	92.53 ± 15.24	93.12 ± 11.13	98.00 (8.50)	98.00 (7.50)	0.478
SRT mean latency (ms)	708.70 ± 517.62	675.95 ± 354.58	491.76 (485.52)	590.04 (442.00)	0.497
SRT latency standard deviation (ms)	293.94 ± 199.77	338.34 ± 216.53	244.95 (300.57)	319.94 (300.64)	0.290
CAMCOG verbal fluency ^a	10.52 ± 6.02	11.33 ± 5.68	10.00 (10.00)	12.00 (8.00)	0.462
Tower of London	7.64 ± 2.70	7.27 ± 3.08	8.00 (2.00)	9.00 (3.00)	0.879
Cats and frogs Stage 1	87.60 ± 21.42	92.89 ± 15.18	100.00 (18.18)	100.00 (8.33)	0.284
Cats and frogs Stage 2	80.36 ± 27.45	79.33 ± 27.11	91.67 (33.33)	100.00 (41.25)	0.952
Cats and frogs Stage 3	65.49 ± 20.03	68.37 ± 23.22	54.86 (35.79)	59.43 (48.00)	0.497
Finger nose pointing ^a	10.88 ± 5.48	11.14 ± 4.94	11.00 (8.00)	10.00 (8.00)	0.790
NEPSY-II visuomotor precision train and car	15.83 ± 4.97	15.97 ± 5.57	18.00 (5.00)	18.00 (5.00)	0.528
NEPSY-II visuomotor precision car and motorbike ^a	17.38 ± 9.83	16.63 ± 9.46	18.00 (17.00)	18.00 (15.00)	0.675
Finger sequencing ^a	238.08 ± 65.57	225.23 ± 59.31	250.50 (80.25)	241.00 (68.00)	0.352

Table 8. Comparing cognitive test scores between males and females for adults aged 16-35. All group comparisons used Mann Whitney U tests aside from ^a when Student's t-tests were used as data did not deviate from normality.

	Mean ± SD	Median (IQR)			p
	Males	Females	Males	Females	
Short ABS Total score	77.69 ± 20.34	80.17 ± 19.29	79.50 (35.25)	84.50 (22.00)	0.563
Short ABS Personal self-sufficiency	28.95 ± 4.66	28.88 ± 4.48	31.00 (7.00)	30.00 (4.00)	0.704
Short ABS Community self-sufficiency ^a	27.24 ± 10.24	28.17 ± 10.53	27.00 (17.00)	30.00 (14.50)	0.625
Short ABS Personal-social responsibility	21.84 ± 7.01	23.13 ± 5.99	22.00 (12.00)	25.00 (7.00)	0.384
DLD Sum of cognitive score	9.00 ± 8.74	6.28 ± 7.95	5.00 (14.00)	3.00 (8.75)	0.041
DLD Sum of social scores	9.16 ± 6.50	9.47 ± 7.20	8.50 (8.00)	8.50 (6.50)	0.985
OMQ Total score ^a	77.93 ± 19.24	72.16 ± 17.42	79.00 (26.00)	71.50 (20.25)	0.089
BRIEF-A Total score ^a	121.29 ± 28.01	120.81 ± 24.98	118.00 (41.00)	121.50 (24.25)	0.922
BRIEF-A Behavioural regulation index ^a	50.83 ± 12.59	50.68 ± 12.19	49.00 (18.25)	49.00 (16.00)	0.948
BRIEF-A Metacognition index ^a	71.33 ± 18.14	69.90 ± 15.56	71.00 (25.00)	70.00 (15.50)	0.653

Table 9. Comparing informant scores between males and females for adults aged 16-35. All group comparisons used Mann Whitney U tests aside from ^a when Student's t-tests were used as data did not deviate from normality.

	KBIT-2 verbal score	KBIT-2 non-verbal score	PAL first trial memory score	Object memory immediate	Object memory delayed	Memory for sentences	Arena	IED levels complete	SRT mean latency	SRT latency standard deviation
KBIT-2 verbal score	-	0.651** (<i><0.001</i>)	0.581** (<i><0.001</i>)	0.488*** (<i><0.001</i>)	0.394** (<i><0.001</i>)	0.827*** (<i><0.001</i>)	0.133 (0.262)	0.409*** (<i><0.001</i>)	- 0.506** (<i><0.001</i>)	- 0.583*** (<i><0.001</i>)
KBIT-2 non-verbal score	-	-	0.636** (<i><0.001</i>)	0.448*** (<i><0.001</i>)	0.460** (<i><0.001</i>)	0.510*** (<i><0.001</i>)	0.243 (0.039)	0.387*** (<i><0.001</i>)	- 0.530** (<i><0.001</i>)	- 0.533*** (<i><0.001</i>)
PAL first trial memory score	-	-	-	0.522*** (<i><0.001</i>)	0.450** (<i><0.001</i>)	0.467*** (<i><0.001</i>)	0.171 (0.157)	0.392*** (<i><0.001</i>)	- 0.489** (<i><0.001</i>)	- 0.614*** (<i><0.001</i>)
Object memory immediate	-	-	-	-	0.536** (<i><0.001</i>)	0.342*** (<i><0.001</i>)	0.043 (0.728)	0.220* (0.027)	- 0.358** (<i><0.001</i>)	- 0.405*** (<i><0.001</i>)
Object memory delayed	-	-	-	-	-	0.264** (0.008)	0.115 (0.353)	0.174 (0.083)	-0.238* (0.020)	-0.250* (0.014)
Memory for sentences	-	-	-	-	-	-	0.172 (0.155)	0.256* (0.011)	- 0.387** (<i><0.001</i>)	- 0.391*** (<i><0.001</i>)
Arena	-	-	-	-	-	-	-	0.108 (0.371)	-0.265* (0.028)	-0.223 (0.065)
IED levels complete	-	-	-	-	-	-	-	-	0.288* (0.004)	- 0.366*** (<i><0.001</i>)
SRT mean latency	-	-	-	-	-	-	-	-	-	0.888*** (<i><0.001</i>)
SRT latency standard deviation	-	-	-	-	-	-	-	-	-	-

	Verbal fluency	Tower of London	Cats and frogs Stage 3	Finger nose pointing	NEPSY-II visuomotor precision train and car	NEPSY-II visuomotor precision car and motorbike	Finger sequencing	Age
KBIT-2 verbal score	0.694*** (<i><0.001</i>) ^a	0.429*** (<i><0.001</i>)	0.568*** (<i><0.001</i>)	0.592*** (<i><0.001</i>) ^a	0.407*** (<i><0.001</i>)	0.515*** (<i><0.001</i>)	0.375*** (<i><0.001</i>) ^a	0.040 (0.662)
KBIT-2 non-verbal score	0.503*** (<i><0.001</i>)	0.380*** (<i><0.001</i>)	0.541*** (<i><0.001</i>)	0.563*** (<i><0.001</i>)	0.323*** (<i><0.001</i>)	0.502*** (<i><0.001</i>)	0.490*** (<i><0.001</i>)	-0.107 (0.240)
PAL first trial memory score	0.442*** (<i><0.001</i>)	0.522*** (<i><0.001</i>)	0.495*** (<i><0.001</i>)	0.584*** (<i><0.001</i>)	0.468*** (<i><0.001</i>)	0.539*** (<i><0.001</i>)	0.334** (0.003)	-0.181 (0.060)

Object memory immediate	0.430*** (<i><0.001</i>)	0.261** (0.008)	0.277* (0.012)	0.385*** (<i><0.001</i>)	0.207* (0.032)	0.380*** (<i><0.001</i>)	0.250* (0.027)	0.038 (0.692)
Object memory delayed	0.281** (0.003)	0.298** (0.002)	0.302** (0.006)	0.291** (0.002)	0.341*** (<i><0.001</i>)	0.428*** (<i><0.001</i>)	0.121 (0.293)	0.002 (0.980)
Memory for sentences	0.593*** (<i><0.001</i>)	0.229* (0.022)	0.482*** (<i><0.001</i>)	0.373*** (<i><0.001</i>)	0.226* (0.020)	0.334*** (<i><0.001</i>)	0.334** (0.002)	-0.089 (0.360)
Arena	0.149 (0.214)	-0.047 (0.699)	0.066 (0.598)	0.126 (0.288)	-0.010 (0.934)	0.075 (0.526)	0.284* (0.017)	-0.005 (0.968)
IED levels complete	0.372*** (<i><0.001</i>)	0.302** (0.002)	0.305** (0.006)	0.406*** (<i><0.001</i>)	0.241* (0.012)	0.286** (0.003)	0.194 (0.085)	-0.048 (0.621)
SRT mean latency	- 0.426*** (<i><0.001</i>)	-0.271** (0.006)	- 0.406*** (<i><0.001</i>)	- 0.539*** (<i><0.001</i>)	-0.296** (0.002)	-0.402*** (<i><0.001</i>)	-0.628*** (<i><0.001</i>)	0.115 (0.239)
SRT latency standard deviation	- 0.472*** (<i><0.001</i>)	- 0.433*** (<i><0.001</i>)	- 0.485*** (<i><0.001</i>)	- 0.572*** (<i><0.001</i>)	-0.320** (0.001)	-0.438*** (<i><0.001</i>)	-0.608*** (<i><0.001</i>)	0.036 (0.714)
Verbal fluency	-	0.331*** (<i><0.001</i>)	0.391*** (<i><0.001</i>)	0.600*** (<i><0.001</i>) ^a	0.461*** (<i><0.001</i>)	0.476*** (<i><0.001</i>)	0.428*** (<i><0.001</i>) ^a	-0.059 (0.529)
Tower of London	-	-	0.235* (0.034)	0.389*** (<i><0.001</i>)	0.410*** (<i><0.001</i>)	0.505*** (<i><0.001</i>)	0.343** (0.002)	-0.024 (0.797)
Cats and frogs Stage 3	-	-	-	0.379*** (<i><0.001</i>)	0.311** (0.004)	0.360** (0.001)	0.252* (0.030)	0.029 (0.792)
Finger nose pointing	-	-	-	-	0.530*** (<i><0.001</i>)	0.524*** (<i><0.001</i>)	0.586*** (<i><0.001</i>) ^a	-0.083 (0.373)
NEPSY-II visuomotor precision train and car	-	-	-	-	-	0.701*** (<i><0.001</i>)	0.383*** (<i><0.001</i>)	-0.043 (0.637)
NEPSY-II visuomotor precision car and motorbike	-	-	-	-	-	-	0.376*** (<i><0.001</i>)	-0.014 (0.877)
Finger sequencing	-	-	-	-	-	-	-	-0.061 (0.583)

Table 10. Correlations between cognitive test outcome scores and age across adults aged 16-35. Values given are correlation coefficients (p values); *p<0.05, **p<0.01, ***p<0.001. All correlations used were Spearman's rho apart from ^a when Pearson's correlation was used as data do not deviate from normality. Values in italics represent correlation coefficients greater than 0.50.

	Short ABS Personal self-sufficiency	Short ABS Community self-sufficiency	Short ABS Personal-social responsibility	OMQ Total score	BRIEF-A Behavioural regulation index	BRIEF-A Metacognition index	Age
Short ABS Personal self-sufficiency	-	0.719*** (<i><0.001</i>)	0.687*** (<i><0.001</i>)	- 0.426** * (<i><0.001</i>)	-0.380*** (<i><0.001</i>)	-0.549*** (<i><0.001</i>)	0.111 (0.230)
Short ABS Community self-sufficiency	-	-	0.762*** (<i><0.001</i>)	- 0.535** * (<i><0.001</i>) ^a	-0.457*** (<i><0.001</i>)	-0.669*** (<i><0.001</i>) ^a	0.162 (0.077)
Short ABS Personal-social responsibility	-	-	-	- 0.631** * (<i><0.001</i>)	-0.572*** (<i><0.001</i>)	-0.731*** (<i><0.001</i>)	0.087 (0.346)

OMQ Total score	-	-	-	-	0.488*** (<i><0.001</i>)	<i>0.741***</i> (<i><0.001</i>) ^a	-0.122 (0.187)
BRIEF-A Behavioural regulation index	-	-	-	-	-	<i>0.643***</i> (<i><0.001</i>)	0.070 (0.452)
BRIEF-A Metacognition index	-	-	-	-	-	-	-0.125 (0.187)

Table 11. Correlations between questionnaire subdomain scores and age across adults aged 16-35. Values given are correlation coefficients (p values); ***p<0.001. All correlations used were Spearman's rho apart from ^a when Pearson's correlation was used as data do not deviate from normality. Values in italics represent correlation coefficients greater than 0.50.

Test	Outcome measure	Comments
PAL	First trial memory score	Ideal for younger adults as wide range with no ceiling effect
	Number of stages complete	Ideal for older adults as small floor effect
IED	Number of stages completed	Ideal for younger adults as can identify subgroups who can complete extra-dimensional shift and who cannot pass any levels
SRT	Latency standard deviation	Ideal for older and younger adults to measure attention as no floor or ceiling effect and accounts for individual variations in motor coordination
Object memory	Immediate memory score	Ideal for younger adults as small ceiling effect and wide range of scores
NEPSY-II visuomotor precision	Car and motorbike score	Ideal for older and younger adults as wide range
Cats and frogs	Stage 3	Ideal for younger adults as small ceiling effect and can identify subgroup able to follow both rules

Box 1. Ideal outcome measures to use in future studies

Cognitive assessment consultee information sheet

A study about how parts of the brain work in people with Down syndrome

Our names are Carla Startin, Sarah Hamburg and Ros Hithersay. We are researchers working at University College London. We are carrying out research to investigate differences in cognitive functions (brain functions) in people with Down syndrome. We will also investigate possible genetic and biological reasons for these differences. The study is funded by the Wellcome Trust, and is sponsored by University College London. The study has been reviewed by the North Wales West Research Ethics Committee.

What is the importance of the study?

People with Down syndrome often differ between one another in their cognitive abilities. These abilities include attention, task planning, memory, language, and co-ordination of movements. Alzheimer's disease occurs more often in individuals with Down syndrome compared to other individuals. Genetic and biological differences may help to explain these cognitive differences in individuals with Down syndrome. This may also explain why some people with Down syndrome develop Alzheimer's disease while others do not.

We are collecting data from a large number of individuals with Down syndrome to investigate some of the reasons that help to explain these differences between individuals with Down syndrome, and why some people with Down syndrome develop Alzheimer's disease and others do not. The results of these studies will hopefully improve the care and treatment of individuals with Down syndrome, and may also help to develop new treatments for Alzheimer's disease.

Participants in this study will be given a variety of brain tasks to investigate their abilities. We will ask participants for a blood sample. We will also ask participants to give a saliva sample. Finally, we will ask participants for a hair sample from their head so that we can investigate how their cells develop. These studies will help us to understand the genetic and biological factors which affect cognitive abilities, and the development of Alzheimer's disease in individuals with Down syndrome.

Who is eligible?

We are looking for people with Down syndrome, aged 16 and older. Participants will need to be able to understand simple instructions and do simple puzzles and games. We will include people who have stable and treated mental or physical health problems. We will not be able to include people who are currently affected by an acute illness, but they will be welcome to take part when they are better.

We will include people who cannot consent themselves. If someone lacks capacity, we have to seek an opinion from a family member or carer (personal or nominated consultee).

What will the study involve?

Participants will take part in an assessment which will last 2 - 3 hours. They will be asked to complete various tests (like games) – some of these will be on a touchscreen computer tablet. Relatives or carers will be asked to be present and will be asked to complete questionnaires during this time. Participants will be given a break half way through the assessment, or more as needed.

We will collect some basic information and medical history about the participants from them and their carers. If agreed, we may also discuss participants with their community learning disability teams and look at their patient records.

We would like to take a photo of the participant. We will check participants' blood pressure and general physical health. We will also take a blood sample for genetic and biomarker analysis, as well as for cellular analysis (e.g. to see how Down syndrome affects cell development). We will take a saliva sample for genetic (DNA) analysis. Finally, we will take a hair sample for cellular analysis. Hair samples will be taken by plucking 6-10 hairs from the scalp. Participants can still take part in the study if they do not want to give blood or hair samples.

Where will assessments be done?

The assessment will be arranged at a time and place that is convenient for the participants. This may include their home or their local day centre or other suitable location. We will reimburse any travel expenses for participants or carers.

What happens after the assessment?

We will give participants a small gift to say thank you for their help. We will tell the participant's GP they have taken part in the study, and we may ask to access their medical records. We will also pass on details of the assessments given to the participants' GP, if requested.

What will happen if we notice anything unusual?

If we notice anything which may be of clinical significance (e.g. if a participant who has not been diagnosed with dementia by the care team has a score suggestive of dementia on the assessment) we will let the care team or GP know. They can then take the appropriate action.

What will happen to the information collected during the study?

All personal information and any information we obtain from our studies will be completely confidential and known only to the research team. All of the results from the study, including the genetic results, will be stored on a database. These will be anonymised (i.e. personal information about participants will not

be stored with any data collected about them). The results may be sent to other researchers or shared with other researchers (these will be anonymised). All personal data will be handled in accordance with the Data Protection Act 1998. Personal data will be password protected and securely held on the UCL IT system or locked in a filing cabinet. Access will be restricted to members of the research team. Personal data will be stored separately from all other data. Personal data will not be disclosed without the consent of the participant (or advice from the consultee if the participant cannot consent). However, if there is a serious risk of harm to the participant, yourself or others, or concerns for the neglect or abuse of the participant, then we will have to share this information with appropriate agencies. This may be without your or the participant's permission. If this happens we would discuss it with you and the participant first. If there are health concerns, the participant's care team or GP may also need to be informed. If this happens we would also discuss it with you and the participant first.

Anonymised paper records will be stored securely within the Faculty of Brain Sciences at University College London. The anonymised information will be entered into an electronic database held within the Faculty of Brain Sciences at University College London. Anonymised cellular data will be entered into an electronic database held within Queen Mary, University of London. Research data will be stored for 20 years following the end of the study, following UCL regulations.

Analysis of the results of the cognitive tasks will be performed within University College London. Blood samples will be stored anonymously and analysed in laboratories within University College London or Queen Mary, University of London, or in some cases in laboratories outside University College London. Saliva samples will be stored anonymously and analysed in laboratories within University College London, or in some cases in laboratories outside University College London. Occasionally the analysis may have to be performed outside the UK. Hair samples will be stored anonymously and analysed in laboratories at Queen Mary, University of London. All biological samples will be anonymised when they are collected. The anonymisation codes will be accessible only to members of the research team, and these will be held securely. Anonymised samples may be shared with other research groups who are researching learning disabilities. Samples may be stored for use in future research. Anonymised genetic data may be shared with other research groups or entered onto publically accessible databases. This is standard practice in genetic studies, and the best way to quickly share information about new genetic findings with other researchers and with clinicians across the world.

We will publish the results from these studies in academic journals, and present them at scientific conferences and meetings. We will keep participants informed about how the study is progressing via a regular newsletter. No participants will be identifiable from any publications arising from the study.

We would like to keep a record of participants' contact details so that we can contact them if we need more information or if we are thinking about doing more research. We will keep this information for ten years following the end of the study.

What are the risks and benefits of the study?

There are few risks to potential participants.

Participants may feel frustrated and anxious when completing the tasks. To reduce this we will have a break in the middle of the session, and we will give further breaks where appropriate.

Giving a blood sample may cause mild pain, some bleeding and bruising. To reduce pain we can use a cream before taking the sample. If a blood test for any medical reason is planned for the future, we can ask the participant's doctor to collect it for us on our behalf at the same time. Collecting a saliva sample may be uncomfortable but should not hurt. Giving a hair sample may also cause discomfort, although this should not last.

This study will benefit individuals with Down syndrome as it will increase knowledge about reasons for differences in those with Down syndrome. This study may also help us to understand how Alzheimer's disease develops. This may lead to better care and treatment of individuals with Down syndrome or Alzheimer's disease in the future.

In addition, the tasks that the participant will complete during this study could be used as a baseline to measure future changes against. If requested we will be happy to share these results with the participant's GP or care team.

Withdrawing from the study

If you decide at any time the participant should withdraw from the study, you have the right to withdraw them and not give a reason. Withdrawing from the study or a decision not to take part will not affect any aspects of care for the participant.

Advice and complaints

If you wish to complain, or have any concerns about any aspect of the way the participant has been approached or treated by members of staff due to their participation in the research, National Health Service (if they were recruited via the NHS) or UCL complaints mechanisms are available to you. Please ask Carla Startin (carla.startin.09@ucl.ac.uk, 020 7679 9314) if you would like more information on this. In the unlikely event that the participant is harmed by taking part in this study, compensation may be available to them. If you suspect that the harm is the result of the Sponsor's (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with Carla Startin, please make the claim in writing to Andre Strydom (a.strydom@ucl.ac.uk, 020 7679 9308), who is the Chief Investigator for the research and is based at UCL. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. The participant may have to bear the costs of the legal action initially, and you should consult a lawyer about this. *NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm.*

Thank you for taking the time to read this information sheet

Please contact us if you have any questions

Details of contact person

Name: Carla Startin
Address: UCL Division of Psychiatry
Division of Psychiatry (Formerly Mental Health Sciences)
6th Floor, Maple House,
149 Tottenham Court Road,
London W1T 7NF
E-mail address: downsyndrome@ucl.ac.uk
Telephone: 020 7679 9314

Cognitive assessment role of consultee information sheet

A study about how parts of the brain work in people with Down Syndrome

As someone who knows _____ (person's name) well/in an independent capacity, you are being invited to consider whether _____ (person's name) would want to participate in the research study based on your knowledge of him/her.

Please could you read this information sheet which outlines the provisions for people who lack capacity to consent to participate in research and the role of the consultee.

The role of a consultee

The role of the consultee is to advise the research team as to the individual's likely wishes/feelings with regard to taking part in the study. The consultee is not being asked to consent on the individual's behalf, but rather to give advice about their wishes. However, the consultee's opinion will be respected in making a decision as to whether the individual should enter the study or not.

If you are prepared to act as the consultee you will be provided with a copy of the participant information sheet and be given an opportunity to discuss the project with one of the researchers so that you can form an opinion as to the individual's likely wishes/feelings in respect to the project. If, at the end of this process, you feel that the individual would like to take part in the project you will be asked to sign a form to that effect.

Capacity to give consent

Usually an adult must give their informed consent before they can be entered into a research study. However, many adults with a learning disability lack the mental capacity to make such a decision. This does not mean that adults who lack capacity must be excluded from taking part in research, but does mean that certain processes - designed to protect both the person lacking capacity and the person making the decision for them - must be followed.

Firstly, it cannot be assumed that an adult with a learning disability lacks capacity to make such a decision. If there is a suspicion that the person lacks capacity, the two stage test of capacity must be applied as set out in the Mental Capacity Act 2005. If, after assessment, the person is deemed not to have the capacity to consent to being entered into the study, then the researcher must appoint a consultee.

Consultees: definition

A consultee can either be **personal** or **nominated**. A **personal consultee** is someone unconnected with the research who knows the potential research

participant in a personal capacity and is able to advise on the person's wishes or feelings. This could be a friend, family member or court appointee.

A **nominated consultee** is someone unconnected with the research appointed by the research team to advise the researcher about the person's wishes or feelings in relation to the project. This could be another professional but they must not have any connection with the study.

The research team has taken reasonable steps to identify a personal consultee in the first instance.

Please contact me if you have any questions.

Thank you for taking the time to read this letter

Details of contact person

Name: Carla Startin
Address: UCL Division of Psychiatry
Division of Psychiatry (Formerly Mental Health Sciences)
6th Floor, Maple House,
149 Tottenham Court Road,
London W1T 7NF
E-mail address: downsyntax@ucl.ac.uk
Telephone: 020 7679 9314

A study about how parts of the brain work in people with Down syndrome



Our names are Carla, Ros and Sarah.



We are doing some **research**

Research is when we ask people questions and do tests to find out things



We are writing to ask if you would like to help us



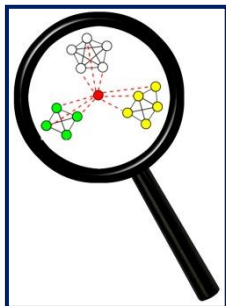
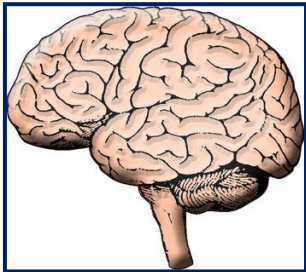
To help you understand this letter you can

- ask someone to read it for you



- talk to your carer about it

What is our work about?



We are finding out about people with Down syndrome

- We want to find out how different parts of the brain work in people with Down syndrome
- We want to find out about differences between people with Down syndrome
- We want to find out if there are genetic or other reasons for this. Genes are like a recipe. They make us who we are.

Why do we want to see you?



We want to talk to you

- because you have Down syndrome
- because you are 16 years old or older

- This research can make things better for people with Down syndrome

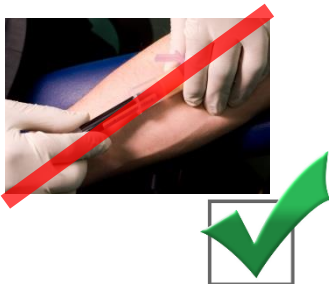
What will happen if you take part?



If you agree to take part

- We will ask you and your carer some **questions**
- We will ask your **care team** some questions

- your carer will fill in some **forms**



- you will do some **tests** – these are like games
- some of the tests will be on a **computer**
- We will check your **health**. We will take your **blood pressure and weight**.
- We will ask you to have a **blood test**
 - the blood test may hurt a little
 - it is **OK** if you do not want the blood test



- We will ask for some of your **spit** (saliva)
 - You can spit into a cup, or we will give you a cup with a small sponge on a stick
 - You put the sponge in your mouth
 - This is to soak up some of your spit (saliva)
 - Then we put the sponge in the cup
- We will **pull a few of your hairs out**
 - pulling a few hairs out may hurt a little

We will **take a photo** of you

The meeting will last for about **3 hours**



We can meet at a place you know like your **home** or at **my work**



Your carer or worker will also come to the meeting

Do you have to take part?



You can tell us **Yes** if you want to take part



You can tell us **No** if you do not want to take part



If you say no it will **not** change the care you get



If you decide to take part, we will ask you to sign a **consent form**



You can stop taking part at any time

What happens after you have seen us?



If you tell us it's **OK** we will



- ask your doctor or care team about you



- tell your doctor about the tests we did
- tell your care team about the tests we did



We will test your blood, spit, or hair in a laboratory

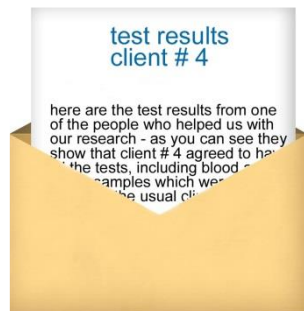
- we may keep them in the laboratory for more tests
- we may need to send them to another place so that they can look at them
- the samples will not be stored with your name





We will also put the test results on a computer

- other people can then look at the information

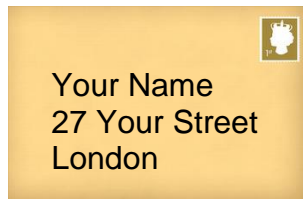


But they will not know it is about you – we will take out your name and where you live (**personal information**) before it goes on the computer



We will give you a **small gift** to say thank you

We will also give you any travel expenses from taking part



If you take part in our study

- the information you give will be confidential
- we will not talk to anyone else about you without asking you first
- we will not use any information with your name and address

We might have to tell someone if we are worried about your health or care at all though

But we would like to keep your name and address on a list

This is so we can contact you if we



need

- more information
- to do more research

If you want to talk to us



you can phone us

or



you can email us



- if you would like to take part in the study



- if you have any questions about the study



- if you are unhappy about something

our phone number is

020 7679 9314

our email address is

downsyndrome@ucl.ac.uk

If you are unhappy about something, you can also talk to your local PALS team

Thank you for looking at this

This research project has been reviewed by the North Wales West Research Ethics Committee. They are there to make sure you are treated well.

Cognitive assessment consultee consent form

A study about how parts of the brain work in people with Down syndrome

Participant Identification Number:

As someone who knows _____ (person's name) well/in an independent capacity, you are being invited to consider whether _____ (person's name) would want to participate in the research study based on your knowledge of him/her.

We ask you to be a consultee because _____ (person's name) is unable to understand the information provided in the information sheet or is unable to make independent decisions and communicate them.

It is up to you to decide whether or not they would want to take part based on your knowledge of the person and the information you have been given. Be reassured that even if you decide that they can take part, he/she is still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect any aspects of their care.

This project has been approved by the North Wales West Research Ethics Committee, and is funded by the Wellcome Trust.

If you have any questions about the study you can contact Carla Startin at downsyndrome@ucl.ac.uk or 020 7679 9314.

	Please initial if you agree
I have read the information sheet about the research. I have had a chance to ask questions and talk about this study. I have got enough information about this study and I understand what the study will involve.	
I confirm that I have agreed to act as a consultee for the above named person. I understand that my role as consultee is to advise the research team as to the above named persons' likely wishes and feelings in relation to entering the study.	
I understand that the participant can stop taking part in this study at any time and does not have to give a reason. I understand that participation in the study will	

not change the care that the participant receives.	
I understand that some of the participant's personal information will be processed during this study, and such information will be stored securely, treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.	
I understand that the data collected during this study will be a part of scientific publications. Confidentiality and anonymity will be maintained for such publications, and it will not be possible to identify the participant from any publications.	
I understand that the research team may contact the participant in the future to participate in follow up studies. Any information collected in the present study may be used in follow up studies.	

Are you aware of any advance directives that may be relevant to participation in this research? If yes, please detail further:	Yes/No
	Please initial if you agree
It is appropriate for _____ to participate in this study	
It is appropriate to take a photo of _____	
It is appropriate for _____ to have their blood pressure and general health checked	
It is appropriate for _____ to have a blood test for genetic, biomarker and cellular analysis	
It is appropriate for _____ to give a sample of saliva for genetic analysis	
It is appropriate for _____ to give a hair sample for cellular analysis	
I agree that their blood, saliva, DNA, or hair can be sent to other researchers (this will be anonymised)	
I agree that their samples can be stored for use in future research	

I agree that their test results can be stored on a database	
I agree that their test results can be shared with other researchers, including publically accessible databases (these will be anonymised)	
It is appropriate for the researcher to discuss _____ with their care team and for their medical records to be accessed	
It is appropriate for the researcher to inform their GP about their inclusion in the study and to potentially send their GP a summary of the findings	
It is appropriate for the researcher to get in touch with them again if they need to	

Any further comments or preferences from the consultee:

Signed:

Name in block capitals:

Date:

Relationship to participant:

Researcher's signature:








Name in block capitals:









Date:









Cognitive assessment participant consent form









A study about how parts of the brain work in people with Down syndrome






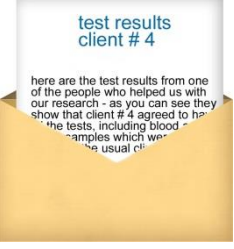


Participant Identification Number:







Please cross no  or tick yes  for each part			
	I have read the information sheet about the research		
	I can understand the information sheet		
	I could ask questions if I wanted to		







Please cross no  or tick yes  for each part			
	<p>I understand that it is my choice to take part in this study</p>		
	<p>I understand that I can say no at any time if I want to stop</p>		
	<p>I understand that taking part will not change the care I get</p>		
	<p>You can ask my doctor or care team about me</p> <p>You can look at my doctor's notes</p>		

Please cross no  or tick yes  for each part		
 <p>I agree to take part in this study</p> 		
 <p>You can check my blood pressure and general health</p>		
 <p>I agree to have a blood test</p>		

Please cross no  or tick yes  for each part			
	<p>I agree to spit in the cup or you can put the sponge in my mouth</p>		
	<p>I agree you can pull a few of my hairs out</p>		
	<p>You can send my blood, spit or hair to other researchers – they will not know my name</p>		
	<p>You can take a photo of me</p>		

Please cross no  or tick yes  for each part			
	<p>You can store my test results on a computer</p>		
	<p>You can share my test results with other researchers – they will not know my name</p>		
	<p>You can share my test results with my doctor and tell them I took part in the study</p>		
	<p>You can share my test results with my care team</p>		

Please cross no  or tick yes  for each part			
	<p>You can keep my blood, spit or hair in the laboratory for more tests</p>		
	<p>You can get in touch with me again for more tests</p>		

	<p>my name</p>	<p>my signature</p> 
	<p>date</p>	
	<p>researcher's name</p>	<p>their signature</p> 
	<p>date</p>	

A study about how parts of the brain work in people with Down syndrome

My name is Carla Startin. I am a researcher working at University College London. I am carrying out research to investigate differences in cognitive functions (brain functions) in people with Down syndrome. I will also investigate possible genetic and biological reasons for these differences. The study is funded by the Wellcome Trust and the Baily Thomas Charitable Fund, and is sponsored by University College London. The study has been reviewed by the North Wales West Research Ethics Committee.

What is the importance of the study?

People with Down syndrome often differ between one another in their cognitive abilities. These abilities include attention, task planning, memory, language, and co-ordination of movements. Alzheimer's disease occurs more often in individuals with Down syndrome compared to other individuals. Differences in brain activity may help to explain these differences in individuals with Down syndrome. This may also explain why some people with Down syndrome develop Alzheimer's disease while others do not.

We are collecting data from a large number of individuals with Down syndrome to investigate brain activity to help to explain these differences between people with Down syndrome. This may also explain why some people with Down syndrome develop Alzheimer's disease and others do not. The results of these studies will hopefully improve the care and treatment of individuals with Down syndrome, and may also help to develop new treatments for Alzheimer's disease.

Participants in this study will be asked if we can place a special cap on their head for us to look at their brain activity. This cap contains electrodes, and we will ask participants to sit as still as possible while we record their brain activity. These studies will help us to understand whether differences in brain activity can explain the differences in abilities and the development of Alzheimer's disease in individuals with Down syndrome.

We would also like to monitor participants' sleep patterns, through the use of a sleep diary and by them wearing a special bracelet during the night which records when they are asleep.

Who is eligible?

We are looking for people with Down syndrome, aged 16 and older. Participants will need to be able to understand simple instructions. We will include people who have stable and treated mental or physical health problems. We will not be

able to include people who are currently affected by an acute illness, but they will be welcome to take part when they are better.

We will include people who cannot consent themselves. If someone lacks capacity, we have to seek an opinion from a family member or carer (personal or nominated consultee).

What will the study involve?

Participants will take part in an assessment which will last around 2 hours. We will measure their brain activity for about twenty minutes.

Relatives or carers are welcome to be present during the assessment.

Participants will also be given a bracelet, which they will be asked to wear for a week. We would also like participants or their carers to keep a sleep diary for this period.

Where will assessments be done?

The assessment will take place at University College London. We will reimburse any travel expenses for participants or carers. We will arrange the assessment at a time that is convenient for the participants.

What happens after the assessment?

We will give participants a small gift to say thank you for their help. We will tell the participant's GP they have taken part in the study. We will also pass on details of the assessments given and results to the participants' GP, if requested.

What will happen if we notice anything unusual?

If we notice anything which may be of clinical significance, we will let the care team or GP know. They can then take the appropriate action.

What will happen to the information collected during the study?

All personal information and any information we obtain from our studies will be completely confidential and known only to the research team. All of the results from the study will be stored on a database. These will be anonymised (i.e. personal information about participants will not be stored with any data collected about them). The results may be sent to other researchers or shared with other researchers (these will be anonymised). All personal data will be handled in accordance with the Data Protection Act 1998. Personal data will be password protected and securely held on the UCL IT system or locked in a filing cabinet. Access will be restricted to members of the research team. Personal data will be stored separately from all other data. Personal data will not be disclosed without the consent of the participant (or advice from the consultee if the participant cannot consent). However, if there is a serious risk of harm to the participant, yourself or others, or concerns for the neglect or abuse of the participant, then we will have to share this information with appropriate

agencies. This may be without your or the participant's permission. If this happens we would discuss it with you and the participant first. If there are health concerns, the participant's care team or GP may also need to be informed. If this happens we would also discuss it with you and the participant first.

Anonymised paper records will be stored securely within the Faculty of Brain Sciences at University College London. The anonymised brain activity data and recordings will be entered into an electronic database held within the Faculty of Brain Sciences at University College London. Research data will be stored for 20 years following the end of the study, following UCL regulations.

Analysis of the results of the assessment will be performed within University College London. All results will be anonymised, and the anonymisation codes will be accessible only to members of the research team. These will be held securely. Anonymised data may be shared with other research groups who are conducting research in the field of learning disabilities.

We will publish the results from these studies in academic journals, and present them at scientific conferences and meetings. In addition, we will keep the participants informed about how the study is progressing via a regular newsletter. No participants will be identifiable from any publications arising from the study.

We would like to keep a record of participants' contact details so that we can contact them if we need more information or if we are thinking about doing more research. We will keep this information for ten years following the end of the study.

What are the risks and benefits of the study?

There are few risks to potential participants.

Participants are required to sit as still as possible during the recording of brain activity. This may be uncomfortable. To minimise any discomfort felt this recording will only last for around twenty minutes, and there will be breaks during the recording.

This study will benefit individuals with Down syndrome as it will increase knowledge about reasons for differences in those with Down syndrome. This study may also help us to understand how Alzheimer's disease develops. This may lead to better care and treatment of individuals with Down syndrome or Alzheimer's disease in the future.

In addition we will be able to use the brain activity recordings as a baseline to measure future changes against. If requested we will be happy to share these results with the participant's GP or care team.

Withdrawing from the study

If you decide at any time the participant should withdraw from the study, you have the right to withdraw them and not give a reason. Withdrawing from the study or a decision not to take part will not affect any aspects of care for the participant.

Advice and complaints

If you wish to complain, or have any concerns about any aspect of the way the participant has been approached or treated by members of staff due to their participation in the research, National Health Service (if they were recruited via the NHS) or UCL complaints mechanisms are available to you. Please ask Carla Startin (carla.startin.09@ucl.ac.uk, 020 7679 9314) if you would like more information on this. In the unlikely event that the participant is harmed by taking part in this study, compensation may be available to them. If you suspect that the harm is the result of the Sponsor's (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with Carla Startin, please make the claim in writing to Andre Strydom (a.strydom@ucl.ac.uk, 020 7679 9308), who is the Chief Investigator for the research and is based at UCL. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. The participant may have to bear the costs of the legal action initially, and you should consult a lawyer about this. *NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm.*

Thank you for taking the time to read this information sheet

Please contact me if you have any questions

Details of contact person

Name: Carla Startin
Address: UCL Division of Psychiatry
Division of Psychiatry (Formerly Mental Health Sciences)
6th Floor, Maple House,
149 Tottenham Court Road,
London W1T 7NF
E-mail address: downsyntax@ucl.ac.uk
Telephone: 020 7679 9314

A study about how parts of the brain work in people with Down syndrome



Our names are Carla and Sarah



We are doing some **research**

Research is when we ask people questions and do tests to find out things



We are writing to ask if you would like to help us



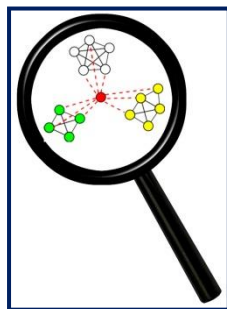
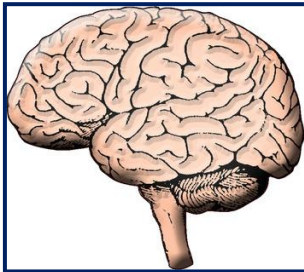
To help you understand this letter you can

- ask someone to read it for you



- talk to your carer about it

What is our work about?



We are finding out about people with Down syndrome

- We want to find out how different parts of the brain work in people with Down syndrome
- We want to find out about differences between people with Down syndrome
- We want to find out possible reasons for this

Why do we want to see you?



We want to talk to you

- because you have Down syndrome
- because you are 16 years old or older

- This research can make things better for people with Down syndrome

What will happen if you take part?



If you agree to take part

- We will put a special cap on your head to make brain traces
- These let us see what's happening in your brain

We will ask you to wear a special



bracelet while you're asleep



The meeting will last for about **2 hours**



We will meet at our **work**



Your carer or worker will also come to the meeting

Do you have to take part?



You can tell us **Yes** if you want to take part



You can tell us **No** if you do not want to take part



If you say no it will **not** change the care you get



If you decide to take part, we will ask you to sign a **consent form**



You can stop taking part at any time

What happens after you have seen me?

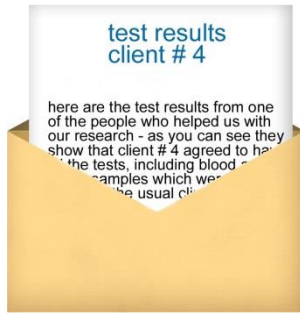


If you tell us it's **OK** we will

- tell your doctor about the tests we did
- tell your care team about the tests we did

We will also put the test results on a computer

- other people can then look at the information



But they will not know it is about you – we will take out your name and where you live (**personal information**) before it goes on the computer



We will give you a **small gift** to say thank you

We will also give you any travel expenses from taking part



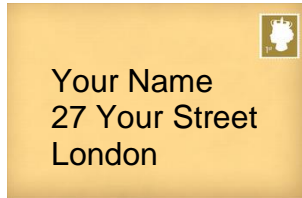
If you take part in our study



- the information you give will be confidential
- we will not talk to anyone else about you without asking you first
- we will not use any information with your name and address



We might have to tell someone if we are worried about your health or care at all though



But we would like to keep your name and address on a list



This is so we can contact you if we need

- more information
- to do more research

If you want to talk to us



you can phone us

or

you can email us



- if you would like to take part in the study



- if you have any questions about the study

- if you are unhappy about something

our phone number is

020 7679 9314

our email address is

downsyndrome@ucl.ac.uk

If you are unhappy about something, you can also talk to your local PALS team

Thank you for looking at this

This research project has been reviewed by the North Wales West Research Ethics Committee. They are there to make sure you are treated well.

EEG assessment consultee consent form

A study about how parts of the brain work in people with Down syndrome

Participant Identification Number:

As someone who knows _____ (person's name) well/in an independent capacity, you are being invited to consider whether _____ (person's name) would want to participate in the research study based on your knowledge of him/her.

We ask you to be a consultee because _____ (person's name) is unable to understand the information provided in the information sheet or is unable to make independent decisions and communicate them.

It is up to you to decide whether or not they would want to take part based on your knowledge of the person and the information you have been given. Be reassured that even if you decide that they can take part, he/she is still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect any aspects of their care.

This project has been approved by the North Wales West Research Ethics Committee, and is funded by the Wellcome Trust and the Baily Thomas Charitable Fund.

If you have any questions about the study you can contact Carla Startin at downsyndrome@ucl.ac.uk or 020 7679 9314.

	Please initial if you agree
I have read the information sheet about the research. I have had a chance to ask questions and talk about this study. I have got enough information about this study and I understand what the study will involve.	
I confirm that I have agreed to act as a consultee for the above named person. I understand that my role as consultee is to advise the research team as to the above named persons' likely wishes and feelings in relation to entering the study.	
I understand that the participant can stop taking part in this study at any time and does not have to give a reason. I understand that participation in the study will not change the care that the participant receives.	
I understand that some of the participant's personal information will be processed during this study, and such information will be stored securely, treated as strictly confidential and handled in accordance with the provisions of the Data Protection Act 1998.	
I understand that the data collected during this study will be a part of scientific publications. Confidentiality and anonymity will be maintained for such publications, and it will not be possible to identify the participant from any publications.	
I understand that the research team may contact them in the future to participate in follow up studies. Any information collected in the present study may be used in follow up studies.	

Are you aware of any advance directives that may be relevant to participation in this research? If yes, please detail further:	Yes/No
	Please initial if you agree
It is appropriate for _____ to participate in this study	
It is appropriate to measure their brain activity using a special cap with electrodes in	

It is appropriate for their sleep patterns to be monitored	
I agree that their test results can be stored on a database	
I agree that their test results can be shared with other researchers, including publically accessible databases (these will be anonymised)	
It is appropriate for the researcher to discuss _____ with their care team	
It is appropriate for the researcher to inform their GP about their inclusion in the study and to potentially send their GP a summary of the findings	
It is appropriate for the researcher to get in touch with them again if they need to	

Any further comments or preferences from the consultee:

Signed:

Name in block capitals:

Date:

Relationship to participant:

Researcher's signature:








Name in block capitals:









Date:







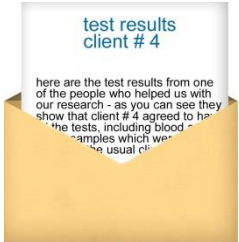

EEG assessment participant consent form





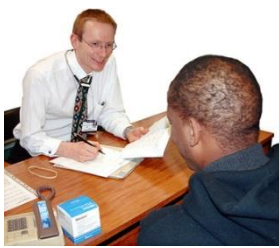

A study about how parts of the brain work in people with Down syndrome







Participant Identification Number:

Please cross no  or tick yes  for each part			
	I have read the information sheet about the research		
	I can understand the information sheet		
	I could ask questions if I wanted to		

Please cross no  or tick yes  for each part			
	<p>I understand that it is my choice to take part in this study</p>		
	<p>I understand that I can say no at any time if I want to stop</p>		
	<p>I understand that taking part will not change the care I get</p>		
	<p>I agree you can put a special cap on my head to make brain traces</p>		

Please cross no  or tick yes  for each part			
	<p>I agree to wear the bracelet when I go to sleep</p>		
	<p>You can store my test results on a computer</p>		
	<p>You can share my test results with other researchers – they will not know my name</p>		
	<p>You can share my test results with my doctor and tell them I took part in the study</p>		

Please cross no  or tick yes  for each part			
	You can share my test results with my care team		
	You can get in touch with me again for more tests		

	<p>my name</p>	<p>my signature</p> 
	<p>date</p>	
	<p>researcher's name</p>	<p>their signature</p> 
	<p>date</p>	