A behavioural and electrophysiological investigation of cognitive and executive dysfunction in older adults with Williams syndrome

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ABSTRACT

Williams syndrome (WS) is a rare developmental disorder accompanied by mild–moderate learning difficulties. The literature focusing on older adults with WS is limited, thus the thesis examined cognitive and executive dysfunction in adults with WS aged 35+ years, adopting behavioural and electrophysiological methodologies.

Claims of premature cognitive ageing, investigated with paired-associates paradigms to measure associative memory ability (Chapter 2), were not supported, rather they highlighted atypicalities capitalising on semantic memory and implementing spontaneous semantic encoding strategies. Further investigation of semantic memory (Levels of Processing paradigm, Chapter 3) showed better recall for 'deep' encoded items; however, effect sizes identified atypical access to semantic memory. Importantly, both studies were characterised with greater false alarms and reaction time for rejecting new items, indicative of poor error monitoring, and deficits in executive processes of inhibitory control and attention in WS. Chapter 4 adopted The Sustained Attention to Response Task which is highly sensitive to inhibition and attentional lapse. The WS group showed inhibitory deficits failing to withhold a response, and problems re-engaging attentional control after making an error.

Chapters 5 and 6 investigated the neural mechanisms underpinning attentional / inhibitory deficits, employing the Oddball paradigm (ERP), and analysis of the alpha and beta frequency bands during resting states (EEG). The WS group showed a) compromised early monitoring of perceptual input, and inefficient task irrelevant stimulus evaluation, and b) low EEG alpha power indicative of reduced inhibitory control, atypical topographical distributions, and low variability; the latter is associated with poorer behavioural performance.

Overall, the thesis has demonstrated how cognitive deficits observed in older adults with WS are grounded in atypicalities in the executive processes of attention and inhibition. It has added to theoretical understanding by advancing our knowledge of both the behavioural and eletrophysiological profiles in older adults with WS, and which sub-serve these atypicalities.

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Peer reviewed publications from the thesis to date:

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Greer, J., Hamilton, C., Riby, D. M., & Riby, L. M. (2014). Deeper processing is beneficial during episodic memory encoding for adults with Williams syndrome. *Research in Developmental Disabilities, 35*(7), 1720– 1726.

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Chapter 5:

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AUTHOR'S DECLARATION

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others.

Any ethical clearance for the research presented in this thesis has been approved. Approval has been sought and granted by the Faculty of Health and Life Sciences ethics committee at the University of Northumbria in Newcastle.

I declare that the word count of this thesis is 50,365 words

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DATE: ……

Chapter 1: General Introduction

1: Summary of the thesis

The thesis examines cognition and executive function in older adults with Williams syndrome (WS). To date the literature typically focuses on children, adolescents, and younger adults with WS, with a limited focus on an older cohort. The thesis will attempt to address some of the gaps in the literature by investigating cognition in adults with WS aged 35+yrs and takes a mixed-methods approach to incorporate both behavioural and electrophysiological paradigms. The behavioural section starts by investigating associative memory (AM) performance (Chapter 2), which is known to decline in typically developing older adults. Chapter 3 focuses on the role of semantic deficits during the encoding phase of episodic memory tests, by incorporating a Levels of Processing paradigm. Chapter 4 investigates executive deficits of attention and inhibition that underpin the AM and semantic memory profiles observed in Chapters 2 and 3. In the electrophysiological section, two studies investigate the neural substrates of attention and inhibition. Chapter 5 adopts the three-stimulus Oddball paradigm, employing event-related potential (ERP) techniques. The final empirical chapter (Chapter 6) uses electroencephalography (EEG) methods to investigate atypicalities in the alpha and beta frequency bands during resting states that may also sub-serve executive dysfunction observed in WS.

1.1 General overview of Williams syndrome

Williams syndrome (WS) is a rare genetic developmental disorder, accompanied by mild–moderate learning difficulties, and distinctive neuroanatomical, clinical, behavioural, and cognitive characteristics (Annaz, Hill, Ashworth, Holley, & Karmiloff-Smith, 2011; Bellugi, Lichtenberger, Mills, Galaburda, & Korenberg, 1999; Campbell et al., 2009; Howlin, Davies, & Udwin, 1998; Meyer-Lindenberg, Mervis, & Berman, 2006). The prevalence of WS is typically estimated at 1/20,000 live births (Morris, Demsey, Leonard, Dilts, & Blackburn, 1988; Morris & Mervis, 2000; Schubert, 2009), though a prevalence rate of 1/7,500 is also documented (Strømme, Bjørnstad, & Ramstad, 2002; of note, the Williams Syndrome Foundation uses a current prevalence rate between these figures of 1/18,000). WS is characterised by a range of health problems, the most serious being the cardiac abnormality supravalvular aortic stenosis (SVAS), where the narrowing of arteries restricts blood flow (Nakanishi, Iwasaki, Momma, & Imai, 1996). Also commonplace are renal and gastrointestinal problems such as infantile hypercalcaemia, and musculoskeletal problems including small stature and delayed growth (Morris et al., 1988). Furthermore, individuals with WS have a distinctive facial appearance, distinguished by a distinctive 'elfin-like' facial dysmorphology. These characteristics include a broad brow, flat nasal bridge, short upturned nose, stellate irises, wide mouth, full lips, and dental malocclusion (Martens, Wilson, & Reutens, 2008), though there is variability in the presentation (Ferrero et al., 2010).

Behaviourally, WS can be characterised by high levels of excessive anxiety, preoccupations and obsessions, eating and sleeping difficulties,

hyperactivity and hyperacusis (Annaz et al., 2011; Howlin et al., 1998). Observable from childhood, individuals with WS can be over-sociable, are extremely outgoing, and sensitive to the feelings of others (Klein-Tasman & Mervis, 2003). However, their over-sociable nature can also extend to indiscriminate friendliness with strangers and displays of inappropriate social disinhibition (Bellugi, Järvinen-Pasley, Doyle, Reilly, & Korenberg, 2007; Davies, Udwin, & Howlin, 1998; Jones et al., 2000). This is in contrast to the social withdrawal observed in autism spectrum disorder (ASD) and aversion to social engagements associated with Fragile X syndrome (FXS: Budimirovic et al., 2006). Despite the outgoing nature associated with WS, atypicalities in social functioning of this group are evident. Individuals with WS report social isolation (Porter, Dodd, & Cairns, 2009) and can have problems forming and maintaining peer friendships, especially evident in adulthood (Udwin, Davies, & Howlin, 1996).

1.1.1 Genetic background to Williams syndrome

The cause of WS is due to a sporadic genetic anomaly, with parent-to-child transmission rarely reported (Ewart et al., 1993). Using fluorescence in situ hybridisation (*FISH*) analysis, the genetic basis of WS is due to micro-deletion of ~28 genes on the long arm of chromosome 7 (Osborne & Mervis, 2007) specifically affecting 7q11.23. Notably, deletions of the elastin gene (ELN) lead to structural abnormalities in the elastic fibres of the skin, lungs, and large blood vessels (Donnai & Karmiloff-Smith, 2000), and is directly linked to cardiac abnormalities associated with WS (Tassabehji et al., 1999) as well as the small stature previously mentioned. Identification of the specific genes deleted in WS

is of great interest to researchers when attempting to elucidate the relationship between genes and behaviour in this syndrome. For example, five genes, *FZD3*, *BCL7B (WS-bTRP, WS-bHLH)*, *STX1A*, *LIMK1*, and *CYLN2*, are known to have neuronal expression and therefore draw attention as specific genetic markers of the behavioural and cognitive phenotype (Morris & Mervis, 2000). The role of *LIMK1* is well established as important for neuronal migration / maturation. It is associated with an altered fear response (Meng et al., 2002) and impaired visuo-spatial cognition in WS (Frangiskakis et al., 1996). Research has demonstrated that sequence variation in the *GTF2I* gene impacts negatively on trait anxiety and dorsolateral prefrontal cortex (DLPFC) responsivity to aversive social stimuli (Jabbi et al., 2015). Importantly, a rarer duplication gene (Dup7q11.23; MIM 609757) has been identified whereby individuals have three copies of the same set of genes (Somerville et al., 2005). Whilst WS individuals with the hemizygous depletion present the typically documented pattern of hypersociability and low social anxiety, those with genetic-duplication, including *GTF21*, have very high levels of social anxiety (Mervis et al., 2012), and are more likely to receive an ASD diagnosis (Sanders et al., 2011). Crucially however, research with patients with small deletions emphasises that it is the 'combination' of missing genes that creates the profiles typically associated with WS.

1.1.2 General cognitive profile in Williams syndrome

In the cognitive domain, although there is significant heterogeneity of cognitive function (Porter & Coltheart, 2005), individuals with WS tend to function at the level of mild–moderate intellectual difficulty (Martens et al., 2008; Searcy et al., 2004). The main body of research has focused on children and adolescents

where full-scale IQ (FSIQ) ranges from 40–100 (Bellugi, Lichtenberger, Jones, Lai, & St. George, 2000), and distributed around 60. FSIQ scores under 30 and over 70 in WS are rare (see Martens et al., 2008, for a review).

The disorder has attracted the attention of cognitive scientists primarily due to its distinctive and uneven cognitive profile (Meyer-Lindenberg et al., 2006). From early childhood, clear dissociations in cognitive abilities are evident. A wealth of literature has documented the prominence of impaired visuo-spatial skills (e.g. Bellugi et al., 2000, Jarrold, Phillips, & Baddeley, 2007; Vicari, Bellucci, & Carlesimo, 2005) compared with lesser impairments in face recognition and verbal ability (e.g. Bellugi, Wang, & Jernigan, 1994; Brock, 2007); though always against the general backdrop of cognitive impairment. However, more recent work has emphasised that even in areas of 'relative' proficiency atypical developmental processes are evident. The cognitive profile associated with WS stands in contrast to other developmental disorders such as Down syndrome (DS), which is associated with relatively impaired verbal ability and relative strengths in the visuo-spatial domain (Edgin, Pennington, & Mervis, 2010; Vicari & Carlesimo, 2006). However as noted, verbal abilities in WS are far from intact and the development of language is far from typical. Young children with WS demonstrate a significant delay in their language development (Mervis & Becerra, 2007). Once developmental milestones have been attained, whilst verbal proficiency is considered one of their cognitive strengths (Bellugi et al., 1999), the highly sociable and loquacious nature of this group can give a misleading impression that masks the extent of their learning difficulties. There is also a difference in the developmental trajectory in verbal and visuo-spatial abilities in

WS. Whilst there are time-associated increases in the scores on both tasks, the rate of improvement is greater in the verbal domain which suggests that verbal mental age develops at a faster rate than spatial mental age (Jarrold, Baddeley, Hewes, & Phillips, 2001). Furthermore, some authors propose that improvements in the spatial domain are due to individuals with WS implementing verbal strategies when performing visuo-spatial tasks (Mervis, Robinson, & Pani, 1999).

1.1.3 Dissociation in memory processes

The verbal / spatial dissociations as described are also evident in cognitive processes, though there are inconsistencies in the research regarding the domains relatively more or less impaired. Short-term memory (STM) appears to be impaired in both verbal and visuo-spatial domains; in contrast, long-term memory (LTM) is relatively less impaired in the verbal domain, compared to typically developing (TD) mental age-matched (MA) controls (Vicari, Bellucci, & Carlesimo, 2003; Vicari, Brizzolara, Carlesimo, Pezzini, & Volterra, 1996) and adolescents / young adults with DS (Edgin et al., 2010; Vicari et al., 2005). However, less impaired verbal and spatial STM is also observed (Costanzo, Varuzza et al., 2013; Jarrold, Phillips, & Baddeley, 2007). This may be due to differences in the methodologies adopted and the age of the participants across the studies.

Similarly, inspection of working memory (WM) performance shows the same verbal / spatial dissociation (Costanzo, Varuzza et al., 2013; Jarrold, Baddeley, & Hewes, 1999). Notably, despite making more errors than TD controls on a spatial WM task, individuals with WS demonstrated greater strategy use to

help performance (Rhodes et al., 2010). The impaired performance in visuo-spatial LTM in WS may be a reflection of impaired visuo-spatial WM (Mandolesi et al., 2009), whereas visuo-spatial WM is relatively less problematic in DS (Edgin et al., 2010). Thus, spatial tasks may not be totally spatial in nature, and may also include some verbal element that may facilitate (or alternatively hinder) performance (Mervis et al., 1999). Notably, impairments in WM performance in WS are further exacerbated with a delay between stimulus presentation and the prompt to respond. O'Hearn, Courtney, Street, and Landau (2009) found a delay of 5 seconds between stimulus and response resulted in impaired WM in WS for both visual-object and visuo-spatial targets compared with MA controls. A 2-second delay still resulted in poorer performance; however object identity was less impaired than spatial identity. This suggests there are domain-specific problems with strategic / executive functioning (EF) in WS, but this can be overcome to some extent. But also see Rhodes, Riby, Fraser, and Campbell (2011) who found impaired EF in both verbal and spatial domains.

Comparison of the profile of WS with other developmental disorders is informative; notably the profiles of cognitive and EF are similar to those observed in Attention Deficit Hyperactivity Disorder (ADHD), a neurodevelopmental disorder characterised by impaired attention, hyperactivity, and impulsivity (American Psychiatric Association, 2013; Sonuga-Barke & Taylor, 2015). ADHD has been claimed to be relatively high in terms of co-morbidity in WS (64%, Lefeyer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006) though there is no neurodegenerative link between the two; whereas in DS the prevalence estimates are similar to the typically developing population (6–8%, Dykens,

2007). Evidence for the similarities between WS and ADHD are discussed in more detail in *section 1.1.9.*

1.1.4 Cognitive ageing in Williams syndrome

To date, research with individuals with WS has mainly focused on children and younger adults, but is limited when investigating cognition in an older WS cohort. Therefore much less is known about the age-related changes in the cognitive profile in WS adults. The first descriptions of the disorder were documented in early 1960s (Williams, Barratt-Boyes, & Lowe, 1961); however, as routine genetic testing has only been available since the 1990s (Morris, Thomas, & Greenberg, 1993), it is likely that many older individuals with WS have remained undiagnosed. Equally, the main medical concern that impacts upon life expectancy is the heart defect previously described. Advances in medical care means that many individuals with WS live longer than previously and therefore there is likely to be an increasing number of adults with WS reaching older age. Most individuals with WS require some level of ongoing support and care with their day-to-day living. However, upon reaching adulthood, some are able to live independently and undertake some form of paid or unpaid employment such as gardening, shelf-stacking, and voluntary work in charity shops (Elison, Stinton, & Howlin, 2010). Longitudinal research has highlighted improvements in social skills and adaptive behaviours with increasing age in WS (young adults to middle age), such as self-help and daily living skills (Brawn & Porter, 2014; Elison et al., 2010). Other age-associated declines include behavioural difficulties such as over-distractibility, aggression, and compulsive / ritualised behaviours (Elison et al., 2010).

Understanding age-associated cognitive functioning in WS is important to researchers because this group displays physical characteristics indicative of premature ageing. These include greying of hair in young adulthood, cataracts, and the relatively early onset of skin-ageing (Cherniske et al., 2004; Lenhoff, Wang, Greenberg, & Bellugi, 1997), and motor control problems associated with the typically ageing process (Hocking, Rinehart, McGinley, & Bradshaw, 2009). Cherniske et al. (2004) also highlighted older age-associated medical complications in adults with WS (aged 30–52yrs), including cardiovascular, endocrine, and gastrointestinal systems. These older age-associated physiological and motor control changes lead to the suggestion that premature cognitive ageing may also be a factor of WS, as has been observed in DS, even though those observed in DS might be distinct due to their link to chromosome 21 (Ball, Holland, Treppner, Watson, & Huppert, 2008; Das, Divis, Alexander, Parrila, & Naglieri, 1995). Premature cognitive- and neuropathological ageing is well documented in DS (Lott & Dierssen, 2010), with pre-senile neurodegenerative changes in the formation of neurofibrillary plaques and tangles associated with Alzheimer's disease (AD) found in individuals with DS from ~45 years of age (Coppus et al., 2008), and linked to trisomy 21, the genetic cause of DS (McCarron, McCallion, Reilly, & Mulryan, 2014). Dementia-type illnesses are not typically associated with WS; however pre-senile neuropathological changes, consistent with those found in DS and AD, were found post-mortem in a 35-year-old individual with WS (Golden, Neilsen, Pober, & Hyman, 1995). Furthermore, two individuals (ages undocumented, but <52yrs) have been diagnosed with dementia (Cherniske et al., 2004). These may be

exceptional cases; alternatively these may provide the first neuropathological indication that premature ageing is a factor of WS.

Whilst the research focusing on adults with WS is limited, the available literature suggests that FSIQ improves with age similar to a typically developing population, though always at the level of mild–moderate learning difficulties (Howlin, Elison, Udwin, & Stinton, 2010; Porter & Dodd, 2011). Subtest differences were also found across the time-span, with greater increases in verbal IQ (VIQ) than performance IQ (PIQ) (Howlin et al., 1998; Searcy et al., 2004: Udwin et al., 1996). This is in direct contrast to the pattern observed in other genetic disorders such as DS and FXS, where FSIQ scores decrease with increasing age – into adulthood in DS, and adolescence in FXS (Carr, 1994; Wright-Talamante et al., 1996).

Two pivotal studies provide evidence for age-associated cognitive decline in adults with WS. Devenny et al. (2004) compared WM and episodic memory performance between young and older adults with WS (aged ≤49yrs and ≥50yrs) with individuals of similar age / IQ and with various unspecified forms of intellectual difficulty (ID). WM scores were significantly higher in the younger age groups in both the WS and ID groups, consistent with better WM performance observed in TD younger adults (Brockmole, Parra, Della Sala, & Logie, 2008). However, regression analysis on the data from the free-recall task (a test of episodic memory) found the decline in performance in the WS group occurred at a chronologically earlier age and was steeper than the ID group, indicative of an age-associated decline in episodic memory in older adults with WS. A second

key study also employed an episodic memory task, incorporating an oral list-learning paradigm and a comparison group of individuals with DS (Krinsky-McHale, Kittler, Brown, Jenkins, & Devenny, 2005). The authors found a significant age-associated reduction in performance in both the WS and DS groups, with the number of items recalled decreasing with increasing age. Considering the dissociation of verbal abilities between WS and DS, this suggests that a) adults with WS are impaired on more demanding episodic tasks as this requires conscious retrieval of learned information, and b) they show premature cognitive decline in a domain in which they normally demonstrate relative strengths (Bellugi et al., 2000).

Research adopting recall / recollection paradigms test episodic memory as they require the conscious retrieval of learned information (Salthouse, 2004). Whilst deficits in episodic memory are often found in individuals with learning difficulties including WS (Vicari, Bellucci, & Carlesimo, 2000), a meta-analysis of forty studies investigating episodic memory in intellectual disorders found this to be relatively preserved in WS compared with DS and groups with learning difficulties (Lifshitz, Shtein, Weiss, & Vakil, 2011). Small but non-significant differences were found between WS and TD groups; conversely, large and significant differences were found between individuals with DS and TD controls. The ability to encode and retrieve information improves with age and is influenced by individual knowledge and conceptual development (Kail, 1990, cited by Lifshitz et al., 2011). However episodic memory also places heavy demands on attentional resources (Vicari et al., 2000). Thus, differences between WS and TD chronologically age-matched controls may reflect poorer ability in WS due to

impaired EF. This may outweigh any age-associated ability to encode and retrieve information as is observed in TD individuals (Bjorklund & Douglas, 1997, cited by Lifshitz et al., 2011).

1.1.5 Cognitive ageing in typical developing older adults

There is a wealth of literature documenting the changes in cognitive ageing associated with the typical ageing process. Age-associated declines are observed in memory functions such as episodic memory, prospective memory, and WM (Gopie, Craik, & Hasher, 2011; Grady & Craik, 2000; McFarland & Glisky, 2011; Park et al., 2002; also see Shing et al., 2010, for a review). However differences in memory functioning are also domain-specific, with age-related improvements observed in some processes such as semantic memory (though declines are observed >65yrs), and declines in visual recognition and verbal recall (Nyberg et al., 2003). Also associated with the typical ageing process are dissociations of spared verbal cognition and impaired visuo-spatial cognition, evidenced in STM, WM, and associative memory (AM) paradigms (Chalfonte & Johnson, 1996; Hale et al., 2011; Jenkins, Myerson, Joerding, & Hale, 2000). It has been suggested that the verbal / spatial WM dissociation reflects domain-specific changes that are affected differentially with increasing age, evidenced in both accuracy and reaction time (RT) measures. Compared to younger adults, Bopp and Verhaegen (2007) found larger age-associated effects of reduced accuracy and increased RT by older adults during a visuo-spatial WM task than a verbal WM task. These differences can be attributed to an overall shrinkage of brain volume (e.g. Tisserand & Jolles, 2003); thus global deficits may be due to a reduction in EF processes which are mediated by frontal regions, and also

declines in functioning in structures such as the hippocampus which are associated with spatial cognition and memory (Klencklen, Després, & Dufour, 2012). Interestingly this spared verbal / impaired visuo-spatial memory dissociation observed in TD older adults matches the relative strengths and weaknesses associated with WS (Bellugi et al., 1999).

1.1.6 Associative memory in typically ageing individuals

One specific area of cognitive performance affected by the ageing process is the memory for complex events, referred to as associative memory (AM). This is a type of episodic memory which requires retrieval of single pieces of related information and binding them together. This reduced ability to link information coherently in memory, known as the associative-deficit hypothesis (ADH) (Bender, Naveh-Benjamin, & Raz, 2010; Naveh-Benjamin, 2000; Riby, Perfect, & Stollery, 2004a,b), proposes that older adults show greater deficits in creating and retrieving associations between single units of information (Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003). The retrieval of bound information requires the recollection of items of information that relate to a specific event; in contrast retrieval of a single item from memory does not require the recollection of contextual information and can be the result of a familiarity judgement (Toth & Parks, 2006).

Research investigating the ADH commonly adopts item and paired-associates paradigms in which participants perform familiarity- and recollection-based tasks. Paradigms adopted in AM research include visual and verbal paired-associates (Shing, Werkle-Bergner, Li, & Lindenberger, 2008), face / spatial

location pairs (Bastin & Van der Linden, 2003), and item / location; item / colour pairing (Chalfonte & Johnson, 1996). From this, it is possible to identify whether older adults have greater difficulty in episodic retrieval in general, or whether older adults' poorer AM performance is due to a deficiency binding information into a cohesive memory representation. An age-associated decline in the ability to recall associative information, compared with relatively spared ability to identify single events, is widely documented in the typical ageing literature (e.g. Anderson et al., 2008; Old & Naveh-Benjamin, 2008). The use of strategies, such as priming, at encoding and retrieval has been shown to decrease AM deficits in older adults (Klib & Naveh-Benjamin, 2011; Naveh-Benjamin, Brav, & Levy, 2007). However, as research has consistently demonstrated poorer ability in AM in older adults compared with younger adults, it would also appear that this older cohort has problems implementing intentional associative encoding and recognition strategies (Prull, Dawes, Martin, Rosenberg, & Light, 2006). Indeed, older adults are less likely to self-initiate elaborative encoding strategies (Naveh-Benjamin et al., 2007) especially under conditions of little environmental support (Craik & Rose, 2012). However, older adults' memory for daily routines benefit when contextual support or external memory aids are incorported (Lindenberger & Mayr, 2014), when trained in elaborative semantic encoding strategies (e.g. Kircchoff, Anderson, Barch, & Jacoby, 2012; Naveh-Benjamin et al. 2007) as well as mnemonic, categorization, or narrative story encoding (Gross & Rebok, 2011; Saczynski, Rebok, Whitfield, & Plude, 2007). Notably, older adults who perform better on tasks of EF also demonstrate better recollection ability (Anderson et al., 2008). Linking this with training techniques, a recent meta-analysis of executive control and working memory training found older adults' ability to benefit from

these methods was comparable to younger adults (Karbach & Verjaeghen, 2014).

1.1.7 Associative memory in Williams syndrome

Thus far, there has been little research investigating AM in older adults with WS; however the available literature with younger cohorts suggests that AM processing may be atypical in WS. Making an association between extracts of information (binding them together) has been identified as problematic across the lifespan in WS when linking visual and spatial information (Deruelle, Rondan, Mancini, & Livet, 2006; Vicari et al., 2005). In contrast, performance on syntactic binding in language production (which requires verbal AM processing) appears relatively less problematic compared with TD controls (Clahsen & Almazan, 1998) and individuals with DS (Carlesimo, Marotta, & Vicari, 1997). Similarly, Jarrold, Phillips, and Baddeley (2007) noted deficits in binding across the age-span in individuals with WS compared to MA matched children. A recent study adopting visual and verbal associative recognition paradigms showed spared item recognition but impaired AM in WS adults, compared with MA matched controls (Costanzo, Vicari, & Carlesimo, 2013). However, whilst these studies demonstrate there are problems of binding in WS, these do little to support the claim of age-associated decline in AM. Jarrold, Phillips, and Baddeley (2007) found AM deficits were evident from a relatively young age; thus deficient AM ability in WS may be a factor of their learning difficulties. Also, comparison of AM performance between WS and TD adults may only demonstrate the relative performance of each group, and not be appropriate methodology for identifying

whether premature cognitive ageing is a factor of WS. However as there appear to be deficits in AM in WS, it is important to investigate this further in order to fill the gaps in the literature. This is addressed in Chapter 2.

1.1.8 Cognition and semantic memory

As outlined in the previous section, AM is a type of episodic memory, which falls under the umbrella of declarative memory. The second component of declarative memory is semantic memory. AM requires the retrieval of contextual information and binding it together, thus also may recruit semantic memory processes (see Yonelinas, 2002, for a review). The aforementioned research suggests that, when LTM requires the encoding or retrieval of rich item and contextual information, difficulties are observed for individuals with WS. However, much like the pattern seen in the typically ageing process, this is accompanied by relatively less difficulty with memory for more automatic, overlearned information involving semantic memory (Bellugi et al., 1994; Lee & Binder, 2014).

Inspection of the WS literature reveals inconsistencies in semantic memory ability, with mixed results regarding more and less proficient areas of functioning. For example, picture naming speed, which is a potential measure of the speed of access to semantic memory, is slower overall in participants with WS compared with TD controls; in contrast, word frequency in the WS lexicon and categorical structuring was comparable with TD groups (Thomas et al., 2006), though on tests of semantic fluency (e.g. listing *'apple / orange / banana'* as types of fruit), individuals with WS produce unusual and low-frequency

category exemplars (Bellugi et al., 1994). However, when presented with exemplars from various categories to remember, recall performance is characterised by semantic clustering of the previously studied items (grouping items from the same category), suggesting that individuals with WS successfully use semantic memory to aid episodic memory performance (Bellugi et al., 1994). In a notably less demanding semantic task, semantic priming and naming speed was relatively well preserved when target words were preceded by a semantically related prime (e.g. apple / pear) compared to an unrelated prime (e.g. house / banana) (Tyler et al., 1997). However, individuals with WS also demonstrate impairments on word–picture matching when required to select from semantically related distractors (Temple, Almazan, & Sherwood, 2002).

In contrast, in a semantic fluency study, the ordering of the items by the WS group produced unusual semantic clustering, indicative of a less sophisticated understanding of semantic structures (Jarrold, Hartley, Phillips, & Baddeley, 2000). Thus, despite the evidence demonstrating individuals with WS can put information into semantic networks, the conceptual reorganisation of this information appears to be problematic for this group (Hsu & Tzeng, 2011). This suggests an atypical relationship between LTM and semantic memory in WS (Purser, Thomas, Snoxall, Mareschal, & Karmiloff-Smith, 2011; Vicari et al., 2005), which may be accompanied by atypical inhibitory processes when distinguishing contextual information (Lukács, Pléh, & Racsmány, 2004; Rossen, Klima, Bellugi, Bihrle, & Jones, 1996). Furthermore, impairments in monitoring of responses are observed, evident by the number of repeated exemplars (Jarrold et al., 2000). This latter finding also suggests that atypicalities associated with

semantic ability are not solely due to differences in memory or language skill, but are also linked to other cognitive processes such as EF (Rhodes, Riby, Park, Fraser, & Campbell, 2010; Smith, Gilchrist, Hood, Tassabehji, & Karmiloff-Smith, 2009). In TD individuals, problems inhibiting the irrelevant meaning of a context are associated with semantic processing deficits (Hoenig & Scheef, 2009).

Alternatively, deficient semantic processing in WS may be due to excessive dependence on phonological STM during language acquisition (Thomas & Karmiloff-Smith, 2003; Vicari et al., 1996). Grant et al. (1997) noted that vocabulary acquisition in WS retains a phonologically-based approach which is observed in TD four-year-olds, reflective of a less mature semantic system. Therefore, reduced input of lexical-semantic knowledge may be at the cost of an over-reliance on phonological encoding. One of the few empirical investigations published comparing phonological / semantic encoding in WS found no difference in the number of items recalled on a verbal STM task, irrespective of the encoding condition (Laing et al., 2005), indicative of a trade-off between relatively strong phonological skills and atypical semantic processing. Furthermore WS performance was comparable with TD controls matched for verbal ability. Similar investigations with developmental disorders such as ASD have also found no bias for either phonological or semantic encoding in LTM (Mottron, Morasse, & Belleville, 2001; Toichi & Kamio, 2002). It is useful to compare cognitive performance in WS with ASD as there can be overlaps in the cognitive functioning across these groups (e.g. attention deficits; Tordjman et al., 2012).

The difference in phonological / semantic encoding might be in part explained by the Levels of Processing (LoP) theory (Craik & Lockhart, 1972), which posits that recall is a function of the depth of mental processing. In TD individuals, shallow processing (focusing on perceptual components of the stimuli) leads to a fragile memory trace. Deep processing (e.g. semantic processing) results in a more durable memory trace and enhanced item recall (Craik & Lockhart, 1972). TD individuals benefit from LoP across the lifespan, and it can facilitate memory improvement in older age when memory capacity and episodic memory are known to decline (Grady & Craik, 2000). Chapter 3 adopts a LoP paradigm to elucidate whether adults with WS can benefit from semantic memory during item recall on a more demanding LTM paradigm.

1.1.9 Executive dysfunction in Williams syndrome

The research presented so far has linked episodic and semantic memory deficits in WS with wider cognitive processes, specifically EF of attention and inhibition. Research has identified a wide range of deficits in EF in WS including inhibition (Atkinson et al., 2003; Menghini, Addona, Costanzo, & Vicari, 2010; Mobbs, Eckert, Mills et al., 2007; Porter, Coltheart, & Langdon, 2007), planning (Mobbs, Eckert, Mills et al., 2007), and WM (Rhodes et al., 2010). Also documented are impairments in visual and auditory sustained attention (Atkinson & Braddick, 2010; Menghini et al., 2010), visual selective attention (Cornish, Scerif, & Karmiloff-Smith, 2007; Scerif, Cornish, Wilding, Driver, & Karmiloff-Smith, 2004), and attentional set-shifting (Atkinson, 2000; Rhodes et al., 2010), though there are discrepancies in the literature also with regard to modalities affected (Costanzo, Varuzza et al., 2013; Osório et al., 2012), and vast individual

differences are evident. Specific to the thesis, attentional deficits in WS are observed from a very young age; toddlers with WS frequently fail to differentiate between distractors and targets (cf. FXS; Scerif et al., 2004). Both atypical inhibitory control and attentional processes are associated with many facets of the behavioural and social phenotype in WS, such as social disinhibition (Davies et al., 1998; Jones et al., 2000; Little et al., 2013; Meyer-Lindenberg, Hariri et al., 2005), lack of stranger danger awareness (Frigerio et al., 2006; Järvinen-Pasley et al., 2010), and with their propensity for prolonged face-gazing (Riby et al., 2011), as well as dual tasking and inhibition in the motor domain (Hocking et al., 2013).

As noted earlier in *section 1.1.3* of this chapter, individuals with WS share EF characteristics with individuals who have ADHD (Rhodes et al., 2010; Rhodes, Riby, Matthews, & Coghill, 2011). Important here is the fact that ADHD is a developmental disorder characterised by impaired attention, hyperactivity, impulsivity (American Psychiatric Association, 2013; Sonuga-Barke & Taylor, 2015). It is also characterised by deficits in EF processes including disinhibition and working memory (Coghill, Seth, & Matthews, 2014; but also see Schoechlin & Engel, 2005, for a meta-analysis detailing relatively spared EF in ADHD), which are linked to atypical frontal lobe functioning (Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005; also see Castellanos & Proal, 2012 for a review of other atypical neuropsychological mechanisms subserving behavioural deficits in ADHD). It is worth emphasising the role of WM in individuals with ADHD, as deficits in WM are functionally associated with a variety of everyday difficulties including impairments in

academic attainment (Fried et al., 2016), social skills (Tseng & Gau, 2013), hyperactive behaviour, (Rapport et al., 2009), as well as dysfunction in EF processes such as attention (Kofler, Rapport, Bolden, Sarver, & Raiker, 2010). Research employing functional magnetic-resonance imaging (fMRI) techniques has demonstrated that the executive impairment observed in WS mirrors the patterns seen in ADHD (Mobbs, Eckert, Mills et al., 2007). Participants with WS (aged 15–48yrs) performed a *Go / No Go* measure of sustained attention and inhibition, found dis-engagement of the frontal-striatal networks of the brain which contribute to the complex pattern of social and behavioural deficits associated with WS (Frigerio et al., 2006; Jones et al., 2000). As successful AM and semantic processing, under investigation in Chapters 2 and 3, also require control from executive processes, Chapter 4 will examine the profile of attentional and inhibitory processes in WS. A variety of paradigms have been adopted to investigate attentional and inhibitory processes including *Go / No-Go*, Stroop, and the Sun / Moon inhibition task. The task adopted for Chapter 4 is the Sustained Attention to Response Task (SART; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997), and has been used extensively with TD, clinical, and ageing populations. The SART is a vigilance task which required the participant to respond to a frequent non-target stimulus and withhold a response to an infrequent target stimulus. This enables a comprehensive examination of lapses of attention and inhibition, previously demonstrated to be related to real world activities in other populations, including developmental disorders (e.g. ADHD, as well as traumatic brain injury (TBI); see Smilek, Carriere, & Cheyne, 2010 for discussion).

1.2 Neuroimaging research

So far, the research discussed in this chapter has identified deficits in cognitive processes of AM and semantic memory, and in frontally controlled EF, specifically atypical attentional and inhibitory processing in WS. The electrophysiological section of the thesis will consider the neural processes which sub-serve these behaviours, and include evidence from magnetic-resonance imaging (MRI), functional magnetic-resonance imaging (fMRI), positron-emission technology (PET), event-related potentials (ERP), and electroencephalography (EEG) techniques. As ERP / EEG methodologies are adopted in Chapters 5 and 6, greater emphasis will be placed on these techniques.

1.2.1 Brain structure and cognition in WS

Research has identified neural markers and structural differences in WS that distinguish them from those observed in typical development. MRI research has shown the frontal cortex in WS to be of normal volume compared with posterior regions (Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993), however there is an overall reduction in brain volume in WS (grey matter ~11%, white matter ~18%) compared with typically developing individuals (Thompson et al., 2005). These include reductions in the volume of white and grey matter in the thalamus, occipital, and frontal lobes, compared with TD individuals (Campbell et al., 2009; Reiss et al., 2004). Grey matter density is reduced in subcortical and cortical regions involved in spatial processing, including the superior parietal sulcus and parahippocampal gyri (Jackowski et al., 2009; Reiss et al., 2004). In contrast, disproportionate increases are found in grey matter volume and grey

matter density in subcortical structures and ventral stream regions known to participate in emotion and face processing including the amygdala, orbital and medial prefrontal cortex, anterior cingulate, insular cortex, and superior temporal gyrus (Jabbi et al., 2012; Martens, Wilson, Dudgeon, & Reutens, 2009). Furthermore, there are atypicalities in key structures of subcortical networks associated with social-cognitive processes (Haas et al., 2013).

These differences in brain structure can be linked with the observed behaviours associated with the WS phenotype. The relative strengths of language and face processing in WS engage structures located in the ventral stream. For example, the fusiform face area (FFA) in WS is twice the size of that found in typically developing controls, and may be implicit in their fascination for faces (Golarai et al., 2010; Riby & Hancock, 2009a,b). Furthermore, there are stimuli-specific differences in activation of the FFA in WS; fMRI research found activation in response to face stimuli comparable with CA controls but reduced in response to house stimuli (O'Hearn et al., 2011). Research incorporating fMRI methodology has found atypical activation in response to threatening and non-threatening visual stimuli in prefrontal areas which are linked to the amygdala (Meyer-Lindenberg, Hariri et al., 2005). Similarly, Haas and colleagues (2009) identified heightened amygdala activity in response to happy facial expressions, whereas response to fearful facial expressions was ether attenuated or even absent.

In contrast, dysfunctions in dorsal stream structures, as well as functional and structural abnormalities in the hippocampus are consistent with the impaired

visuo-spatial performance associated with WS (Meyer-Lindenberg, Mervis et al., 2005). This may be due to deficient processing of stimuli by the visuo-spatial regions that project into the hippocampus from dorsal stream regions. [Hippocampal size in WS appears to be preserved, however there are subtle differences in the shape (Meyer-Lindenberg, Mervis et al., 2005).] It may also be exacerbated by the significant reduction in resting cerebral blood flow (CBF) and reduction of biochemical markers of synaptic activity in the anterior hippocampus (Meyer-Lindenberg, Mervis et al., 2005). Furthermore, dissociations in both cortical volume and CBF have been found. Decreases in both cortical volume and CBF are observed in dorsal stream structures, compared with disproportionate increases of both in ventral stream structures (Jabbi et al., 2012). These atypicalities in CBF and cortical volume have also been directly linked with the atypical behavioural and social phenotype observed in WS (Jabbi et al., 2012; Meyer-Lindenberg, Hariri et al., 2005). Of note, it is interesting to observe differences in the neuro-cognitive profiles of DS and WS. A study comparing cognition in DS and TD individuals, found exaggerated deficits in those domains sub-served by the hippocampus (e.g. pattern recognition; paired-associates learning) compared to frontal lobe measures (e.g. verbal and design fluency) (Pennington, Moon, Edgin, Stedron, & Nadel, 2003). Similarly, there are parallels in frontal lobe structure between WS and older adults who are ageing typically (Bartzokis, Beckson, Nuechterlein, Edwards, & Mintz, 2001; Driscoll et al., 2009; Hogan et al., 2011; Raz, Rodrigue, & Acker, 2003; Raz et al., 2005; Tisserand & Jolles, 2003). Therefore, evidence of structural atypicalities and deficits of cognition in other disorders and TD ageing, even without direct comparison to WS, can be informative.

Converging evidence from neuroimaging research including fMRI (Lenartowicz, Verbruggen, Logan, & Poldrack, 2011), PET (Obeso et al., 2013), transcranial magnetic stimulation (TMS; Daskalakis et al., 2008), and lesion methodologies, confirm that response inhibition is sub-served by a network of interconnected frontal cortical regions including the striatum, dorsolateral prefrontal cortex (DLPFC), right inferior frontal gyrus (IFG), dorsal anterior cingulate cortex (dACC), and pre-supplementary motor area (pre-SMA). The performance of tasks that require sustained attention is associated with activation of a predominantly right-lateralised network and includes the DLPFC, the anterior cingulate cortex (ACC), and the right inferior parietal lobule, with top–down modulatory projections to subcortical arousal structures (Sturm & Willmes, 2001). Imaging studies have supported this observation by showing that the right hemispheric sustained attention network is engaged over periods of less than a minute (Paus et al., 1997) and that brief lapses of attention are preceded by momentary reductions of activity in frontal control regions (Weissman, Roberts, Visscher, & Woldorff, 2006). Furthermore, individual differences in the measurement of withholding a response to the target stimuli have been shown to be related to inhibitory ability and impaired frontal lobe function (see Simmonds, Pekar, & Mostofsky, 2008, for a meta-analysis).

1.2.2 ERP profile of associative memory in TD and WS

The aforementioned neuroimaging methodologies have enabled researchers to identify the spatial and functional mapping of fronto-cortical networks recruited during inhibitory processes in both typically and atypically

developing individuals. The temporal precision obtained from ERP methodology complements imaging research by pinpointing with millisecond accuracy the neural responses associated with behavioural performance, and how these differ between populations. For example, the neuroimaging research into AM provides strong support for functional dissociations between familiarity and recollection, identifying distinct spatial-temporal profiles (Diana, Yonelinas, & Ranganath, 2007; also see Yonelinas, 2002, for a review). There are two topographically distinct ERP correlates of recognition memory observed in mid/frontal and parietal regions, and which modulate familiarity and recollection respectively (Rugg & Curran, 2007). Familiarity judgements elicit the frontal FN400 (also referred to as the mid-frontal effect), a negative going component observed ~300–500ms post-stimulus onset, also referred to as the mid-frontal effect (Curran & Hancock, 2007; see Guillaume & Etienne, 2015, for a discussion on difficulties interpreting the functional signifiance of the FN400), with greater negative responses observed bilaterally and mid-centrally to new items compared with old items (Addante, Ranganath, & Yonelinas, 2012; Smith, Riby, Sünram-Lea, van Eekelen, & Foster, 2009; Voss & Paller, 2006). Recollection elicits the parietal P600 (a positive going component observed ~600ms post-stimulus onset) in response to old rather than new items (Curran, 2000; Rugg & Curran, 2007).

Generally, research employing ERP methods in WS is scarce; however two pivotal studies have demonstrated atypical neural correlates of familiarity and recollection in WS. Key and Dykens (2015) found an atypically enhanced frontal FN400 / mid-frontal effect in response to non-social stimuli (houses) compared

with social stimuli (faces), and contrary to the pattern hypothesised. The ERP signature from paired-associates paradigms have not been directly investigated in WS; however there is also evidence for atypical frontal activity in WS when binding information. Grice et al. (2001) found a weaker but more prolonged response in unspecified frontal regions compared to the other groups in response to upright / inverted faces in a WS group despite eliciting the frontal N170 component, which is linked to structural encoding of face stimuli (Blau, Maurer, Tottenham, & McCandliss, 2007), confirming that face orientation was detected.

1.2.3 ERP profile of attentional and inhibitory processing

One paradigm highly sensitive to the ERPs associated with involuntary and voluntary attentional and inhibitory processes is the three-stimulus Oddball task (Donchin, Ritter, & McCallum, 1978). Participants respond to an infrequent target stimulus while withholding their response to two distractors; a frequent non-target stimulus and an infrequent novel stimulus. The Oddball task measures automatic shifts in attention, allocation of controlled attentional resources and context updating in WM (Polich, 2007), and elicits three main ERP components; the N2, P3a, and P3b. The N2 is a negative-going waveform which peaks between ~180–350ms post-stimulus (Daffner, Alperin, Mott, Tusch, & Holcomb, 2015). It is a sensory component thought to represent a controlled mismatch detection processes, thus discriminating between novelty detection and cognitive control (Folstein & Van Petten, 2008) and is associated with the early recognition and parsing of visual information in the environment (Riby & Orme, 2013). The novel N2 evoked when no behavioural response is required (i.e. novel stimuli / *No-Go* response), is reflective of response inhibition, and is typically observed

fronto-centrally. In contrast, the N2 evoked in response to the target stimulus represents the degree of attention that is needed for processing stimuli context, and is typically observed centro-parietally (see Folstein & Van Petten, 2008, for a detailed review on the classification and function of the N2 component). The P3a and P3b are subcomponents of the positive-going P300 waveform, and have different functional correlates (Volpe et al., 2007). The P300 typically peaks between ~250–500ms post-stimulus; with the P3a distributed fronto-centrally, and the P3b distributed centro-parietally (Polich, 2003). The P3a is associated with automatic responses during the engagement of attention, inhibition, and orienting to the environment. As such, it typically elicits a relatively large peak amplitude and relatively short peak latency. The P3a has also been associated with dopaminergic function and attentional control processes (Kähkönen et al., 2002; Riby, 2013). The P3b is associated with the controlled processes required during WM updating, and typically elicits a smaller peak amplitude and longer peak latency, reflecting the greater amounts of attentional resources required for task performance (see Polich, 2007, for a detailed review of the classification and function of the P300 component).

The Oddball paradigm has been used widely in research investigating neural functioning of TD individuals (Barron, Riby, Greer, & Smallwood, 2011), clinical populations (e.g. schizophrenia: del Re et al., 2014), and developmental disorders (e.g. ASD: Cléry et al., 2013). To date the Oddball task as described here has not been employed in research with individuals with WS; however, Key and Dykens (2011) used an Oddball paradigm to investigate global / local stimulus discrimination during a Navon style visuo-spatial task in a group of adults

with WS and CA controls. The WS group's ERP profile was characterised by prolonged P3a latencies in response to both levels, and attenuated P3a amplitude in response to the local stimulus suggesting insufficient allocation of attentional resources to local features. The WS group also showed no P3b discrimination between conditions, whereas the CA group's ERP profile included increased P3b latencies in response to the local targets indicative of impaired effortful processing when greater attentional resources are required, as would be the case during local stimulus discrimination, Other ERP studies also indicate atypical activity in WS in components elicited by the Oddball task (Grice et al., 2001; Haas et al., 2009; Mills et al., 2000) suggesting WS is characterised by an atypical neural signature in both the early sensory / perceptual and later controlled processes.

Inspection of the ADHD and ASD literature has proved promising in elucidating the potential neural mechanisms recruited in WS during an Oddball task (although of course syndrome-specific mechanisms may also be possible). Adults with ADHD present attentional deficits, with attenuated non-target N2 peak amplitude compared to CA controls, and comparable P3a / P3b peak amplitudes latencies, likely reflecting more effortful processing by the ADHD group. In contrast, longer N2 / P3a peak latencies in response to the novel stimulus in ASD suggest delayed orienting to novelty response, and prolonged P3b peak latency reflecting impairments in sustained attention (Sokhadze et al., 2009). However, mixed findings are also observed in both disorders (e.g. Fallgatter et al., 2005; Prox, Dietrich, Zhang, Emrich, & Ohlmeier, 2007; Townsend et al., 2001),

possibly due to the recruitment of differing attentional neural mechanisms during stimulus detection (Crottaz-Herbette & Menon, 2006).

1.2.4 EEG techniques

Complementary to ERP techniques, EEG methodology enables researchers to identify topographical distributions of electro-cortical activity and how these sub-serve general and specific cognitive processes. EEG activity recorded from the scalp is characterised by five distinct frequency bands; delta (.05–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (13–29 Hz), and gamma (30–45 Hz). Whilst it is unlikely that these sub-serve specific cognitive processes in isolation (Engel & Fries, 2010), the thesis focused on the alpha and beta frequencies, as both are functionally associated with attention and inhibiton (Buschman & Miller, 2007; Klimesch, 2012; Palva, Kulashekhar, Hämaäläinen, & Palva, 2011). Specific to the PhD, alpha is a prominent feature of EEG and notably associated with cortical inhibitory processes (Klimesch, Sauseng, & Hanslmayr, 2007), whilst beta has functional association with the allocation of attention, cognitive control, and the action / inhibition of voluntary movements (Kilavik, Zaepffel, Brovelli, MacKay, & Riehle, 2013). Of note, there is evidence that sub-bands of these EEG frequencies have distinct topographical distributions and functional significance. In the alpha band, low-alpha (8–10 Hz) has greater association with general attentional demands and is characterised by a more widespread topographical distribution, whereas upper-alpha (10–12 Hz) has greater task-relevant function (e.g. semantic processing) and a more focal distribution (Doppelmayr, Klimesch, Stadler, Pöllhuber, & Heine, 2002; Klimesch, 1999; Klimesch et al., 2007).

1.2.5 Functional role of the alpha band

The alpha band is primarily associated with attention and inhibitory processes, and the mechanisms of attention and consciousness (for a review, see Palva & Palva, 2007). Unlike the other frequency bands, alpha activity is characterised by an inverse profile whereby an increase in alpha power (synchronisation) is indicative of less cortical activity, whilst a decrease in alpha power (desynchronisation) reflects bottom–up activity in response to visual / sensory input (Bollimunta, Mo, Schroeder, & Ding, 2011; Jensen, Gelfland, Kounios, & Lisman, 2002; Klimesch, 2012; Klimesch et al., 2007). [Of note, alpha desynchronisation has also been observed during opening of the eyes in a darkened room, thus not solely responsive to visual stimulation (Moosman et al., 2003).] Whilst alpha oscillations generally fluctuate as a result of changes in attentiveness, alpha desynchronisation occurs when cognitive and attentional processes are required (Klimesch, 1999), thus task demands seem to be critical. As such, it is more plausible that alpha desynchronisation is also reflective of top–down processing, as this requires the recruitment of attention resources in response to changing task demands (Haegens, Händel, & Jenson, 2011; von Stein, Chiang, & König, 2000).

However, sensory and cognitive processing is not solely characterised by decreasing alpha power; rather, patterns of task-relevant / stimulus-specific alpha synchronisation and desynchronisation are observed. For example, increases and decreases in alpha power are observed in memory paradigms and which are functionally associated with encoding and retrieval. STM (Poliakov, Stokes,

Woolrich, Mantini, & Astle, 2014) and WM (Haegens, Osipova, Oostenveld, & Jensen, 2010) paradigms are accompanied with synchronised alpha activity in the fronto-parietal network during encoding, and desynchronised activity during retrieval. This is thought to reflect a) the inhibition of irrelevant information during encoding, and b) a release of these inhibitory processes at retrieval to facilitate recall (Klimesch, 2012; Klimesch, Fellinger, & Freunberger, 2011; Sauseng et al., 2005, 2009).

Notably, topographical distributions observed in alpha power are concomitant with functional relevance, whereby decreases indicate activation in task-relevant cortical regions whilst simultaneous increases reflect the inhibition of task-irrelevant ones (Klimesch et al., 2007; Palva, Monto, Kulashekhar, & Palva, 2010). During stimulus-response tasks such as the Oddball paradigm decreased alpha power is observed in task-relevant regions post-cue, pre-target, and post-stimulus, and accompanied with increased power in the surrounding cortical regions (Barry, 2009; Rajagovindan & Ding, 2011). Levels of posterior pre-stimulus alpha can predict behavioural performance (Min & Herrmann, 2007; Zhang, Wang, Bressler, Chen, & Ding, 2008). Decreased alpha power prior to an upcoming *No-Go* stimulus signals a release from cortical inhibition thus enabling the cognitive processes required for inhibiting motor actions (De Blasio & Barry, 2013; Dockree et al., 2004). In contrast, brief increases in pre-frontal and posterior pre-stimulus alpha power are associated with attentional lapses and poorer task performance (MacDonald, Mathan, & Yeung, 2011; van Driel, Ridderinkhof, & Cohen, 2012).

1.2.6 Functional role of the beta band

The role of the beta band in cognitive processing is well established with a body of literature emphasising beta activity in top–down visuo-attentional processing (Gross et al., 2004; Kamiński, Brzezicka, Gola, & Wróbel, 2012; Seigel, Donner, & Engel, 2012). Evidence for a functional role of beta was established in the early EEG observations where greater beta power was observed in participants with better visual imagination (Mundy-Castle, 1951, cited in Gola, Magnuski, Szumska, & Wróbel, 2013). Subsequent research identified functionally distinct topographical distributions, whereby beta power in occipito-parietal regions was positively correlated with accuracy scores during visual vigilance tasks (Belyavin & Wright, 1987; Townsend & Johnson, 1979). Research with non-human primates has supported the association between beta activity and attentional processes in both subcortical (e.g. thalamic structures) and cortical regions of the visuo-attentional system (see Wróbel, 2014). A similar pattern is observed in human subjects: a series of studies have demonstrated that greater occipito-parietal beta power is associated with better performance on tasks which recruit attentional processes (e.g. Basile et al., 2007; Kamiński et al., 2012; MacLean, Arnell, & Cote, 2012). In contrast, diverted attention results in attenuated beta, even if a change in stimulus is expected (Todorivic, Schoffelen, van Ede, Maris, & de Lange, 2015).

The beta band is also highly associated with sensorimotor processes, and is characterised by a pattern of increased and decreased power which are functionally associated with the execution and inhibition of voluntary movements (Kilavik et al., 2013). Increased beta activity is observed when voluntary

movements are to be suppressed (Kühn et al., 2004; Zhang et al., 2008), whereas decreased beta activity is observed during the preparation and execution of voluntary movements (Alegre et al., 2006; Tzagarakis, Ince, Leuthold, & Pellizzer, 2010; Wheaton, Fridman, Bohlhalter, Vorbach, & Hallett, 2009). Beta activity also decreases pre-movement and increases post-movement (Kilavik et al., 2013). Pre-movement decreases reflect attentional processes in the preparation of movement (Wheaton, Carpenter, Mizelle, & Forrester, 2008), and 'rebounds' ~300–1000ms after the cessation of the movement (Kilavik et al., 2013) reflecting inhibition of the motor network (Solis-Escalante, Müller-Putz, Pfurtscheller, & Neuper, 2012). Similar to alpha, during response inhibition tasks, increased pre-stimulus beta power predicts successful inhibition in response to *No-Go* stimuli (Swann et al., 2009; Wheaton et al., 2009). In contrast, beta activity post-commission errors is characterised with greater rebound, indicative of increased response inhibition (Koelewijn, van Schie, Bekkering, Oostenveld, & Jensen, 2008).

1.2.7 Alpha and beta – atypical activity and developmental disorders

Atypicalities in alpha and beta activity can be linked to EF deficits in both TD individuals and atypical / clinical populations. For example, a recent study investigating age-associated beta activity during a sustained attention task (Gola et al., 2013) found no overall differences in beta power or task performance that could be attributed to increased age. However, in a sub-group of lower performing elderly adults, identified by greater behavioural deficits in sustained attention, significantly attenuated beta activity was observed when more demanding attentional processing was required compared with the less challenging

conditions. Furthermore, increased alpha activity with greater task difficulty was found in this group, indicative of impaired task-specific alpha desynchronisation (O'Connell et al., 2009).

In ADHD, the EEG profile is typically characterised by an enhanced theta / beta ratio, compared with TD individuals (for a meta-analysis see Arns, Conners, & Kraemer, 2012). Notably, when individual fast wave alpha levels are accounted for, group differences in behavioural performance dissipate, emphasising the relevance of atypical alpha activity in both the EEG and behavioural profiles associated with ADHD (Lansbergen, Arns, van Dongen-Boomsma, Spronk, & Buitelaar, 2011; Woltering, Jung, Liu, & Tannock, 2012). Also, ongoing attenuated low-alpha and enhanced beta power is observed during task duration in ADHD, and with negative correlations in beta power and behavioural variability. This appears to be a compensatory mechanism, notably with increasing task demands, whereby this group requires greater cortical activity to maintain sustained attention and reduce behavioural variability. A similar profile has been described in TBI individuals (Roche et al., 2004). This emphasises the need to include electrophysiological alongside behavioural paradigms in research with individuals with developmental disorders (however, see Thomas and Karmiloff-Smith, 2002 for a discussion of issues when comparing research evidence from developmental disorders with clinical groups such as TBI).

1.2.8 Resting states – Eyes Closed / Eyes Open paradigm

Thus far the research discussed in this section has documented the role of the alpha and beta bands during goal-directed cognitive processing. However,

as demonstrated in the neurodevelopmental literature, under certain task conditions, atypically developing groups and clinical populations can perform as well as TD individuals. As such, trying to elucidate how and why the neural mechanisms and their associated behavioural processes differ between those with developmental disorders and TD individuals can be problematic. Electro-cortical activity whilst unconscious (i.e. during sleep / coma) and during resting states (i.e. relaxed conscious) have distinct profiles that can be dissociated from conscious sensory and cognitive processing (Cirelli & Tononi, 2015; Gosseries et al., 2014; Marzano et al., 2013); thus by studying neural activity in the absence of stimulus-induced / goal-directed activity, researchers can distinguish how cortical and subcortical processes differ between active and passive conditions.

Typically, resting-state activity is recorded by implementing an Eyes Closed (EC; whereby participants rest with their eyes closed), and / or Eyes Open (EO; where they focus on a non-task-related visual stimulus) paradigms. Electro-cortical activity during EC is thought to reflect a general baseline level of arousal, whereas neural activity during EO represents a tonic measure of the metabolic state of activation required for task performance (Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Raichle et al., 2001). On opening the eyes, attenuated cortical and subcortical activity is observed as a response to visual stimulation (Mo, Liu, Huang, & Ding, 2013). This is evidenced by negative correlations between alpha power and blood oxygen-level dependent (BOLD) activity in the visual cortex (Moosman et al., 2003). In contrast, the lack of visual input during EC is reflected in the lack of subcortical structure deactivation and reduced BOLD signal (Laufs et al., 2006; Moosman et al., 2003).

Similarly, specific distributions of EEG frequencies bands are also evident during resting states, with synchronised activity in both the alpha and beta bands typically distributed over parieto-occipital regions during EC (Chen, Feng, Zhao, Yin, & Wang, 2008). Importantly, EEG sub-bands have different EC profiles. Low-alpha has a more widespread topography across anterior–posterior regions, whereas upper-alpha and beta are dominant posteriorly. Opening the eyes results in topographic changes; both alpha and beta bands desynchronise; however the decreases in posterior regions are more pronounced in alpha, whereas smaller posterior decreases and pre-frontal increases are observed in beta, believed to be the engagement of frontally controlled regions responsible for executive processes (Barry et al., 2007; Chen et al., 2008; Klimesch et al., 2007; Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007).

Atypicalities in the resting-state EEG profile are observed in several developmental disorders. For example, significantly attenuated alpha, beta, and gamma are found in adolescents with DS compared with typical MA controls (Babiloni et al., 2009). In ADHD, alpha power is reduced compared with controls during both EC and EO (Woltering et al., 2012), whilst attenuated beta is widely acknowledged in the atypical theta / beta ratio (Arns et al., 2012). In FXS, beta power is comparable to controls, and upper-alpha is significantly attenuated during EC (Van der Molen & Van der Molen, 2013), and which is linked to executive dysfunction such as attentional lapses (cf. WS; Mobbs, Eckert, Mills et al., 2007). However there are mixed findings in ASD literature (Cherkassky, Kana, Keller, & Just, 2006; Coben, Clarke, Hudspeth, & Barry, 2008; Mathewson et al.,

2012; Murias, Webb, Greenson, & Dawson, 2007; for a review, see Wang et al., 2013).

In the WS literature, the focus on EEG methodology is notably lacking compared to other developmental disorders. However, the available EEG research has documented underactivity in the gamma band during face orientation processing (Bernardino, Castelhano, Farivar, Silva, & Castel-Branco, 2013; Grice et al., 2001), reduced alpha / increased beta during sleep (Bódizs, Gombos, & Kóvacs, 2012; Bódizs et al., 2014), and stimulus-selective differentiation in alpha power in response to different musical timbre and happy / sad musical styles (Lense, Gordon, Key, & Dykens, 2014). Thus, in line with other developmental disorders, it would appear that an atypical EEG profile is present in WS under certain conditions. To date, there is only one known study which specifically focuses on the EEG signature in WS during resting states. Adults with WS presented attenuated frontal alpha power in the left hemisphere compared with TD controls, and greater right over left hemispherical asymmetry, whereas greater left over right asymmetry was observed in the TD controls (Ng, Fishman, & Bellugi, 2015). Functionally, the over-recruitment of the left hemisphere may reflect the exaggerated anxieties associated with WS (Dykens, 2003; Klein-Tasman & Mervis, 2003). Notably, as the EC / EO data were combined in the analysis, interpretation of the results needs to be addressed with caution. The final empirical chapter (Chapter 6) in the thesis addressed the methodological issues by investigating EC and EO conditions separately in order to elucidate how these EEG profiles sub-serve the attentional and inhibitory deficits which have been highlighted consistently throughout this chapter.

1.3 Methodological considerations

This final section of the General Introduction will discuss methodological considerations when undertaking research with individuals with developmental disorders. Methodological issues are not exhaustive, thus the most pertinent issues relevant to the thesis are discussed. Please refer to the specific chapters in Van Herwegen and Riby (2015) for discussions on cross-sectional, longitudinal, and developmental trajectory designs.

1.3.1 Group matching

Thus far, this chapter has considered research evidence documenting the behavioural, cognitive, EF, and neurocognitive profiles in WS. In order to understand what the data tell us about these profiles in WS, it is necessary to compare this with some form of control / comparison group. However, there has been much debate in the literature as to the most appropriate method of group matching in research with individuals with developmental disorders (Jarrold & Brock, 2004; Karmiloff-Smith, 2013; Thomas et al., 2006). Researchers have attempted to address these problems by using a variety of matching techniques such as recruiting TD controls for chronological age (CA) and mental age (MA). Matching for CA, whilst informative as to age-associated group differences, can also be irrelevant as individuals with WS typically do not perform at the level of their CA (Porter & Coltheart, 2005).

Alternatively, MA matching is common practice, using standardised parametric tests that measure FSIQ, as well as specific domains of verbal and non-verbal abilities. Popular methods include standardised IQ tests such as the adult and child Weschler tests, as well as parametric tests of specific domains such as verbal fluency, language, and visuo-spatial abilities. Whilst these are psychometrically validated tests, their application has been questioned because of the complexity of developmental disorders such as WS. For example, FSIQ scores do not reflect domain-specific strengths and weaknesses, whilst the fluent verbal abilities in WS may camouflage poor general cognitive performance in other areas. Furthermore, even when these are accounted for, several studies have found scores on verbal / non-verbal subtests did not match the typically expected better VIQ / poorer PIQ (e.g. Farran, Blades, Boucher, & Tranter, 2010; Howlin et al., 1998). Not all standardised tests are suitable for all age ranges, thus caution needs to be taken interpreting the data because of lack of consistency between psychometric tests such as the child and adult versions of the Weschler tests. Also, when TD controls are matched accordingly to the selective deficits relevant to the research paradigm, the study becomes theoretically driven rather than hypothesis driven (Thomas et al., 2009).

1.3.2 Comparisons with other developmental disorders

An alternative method for matching the WS group is to compare them with another developmental disorder. For example, it is useful to compare the cognitive behaviours in WS with ASD as there are overlaps in the cognitive functioning across these groups (Tordjman et al., 2012). Similarly, throughout this chapter, comparisons have been made between WS and ADHD due to the

parallels in the attentional and inhibitory profiles (Rhodes et al., 2011), thus taking a theory-driven comparison approach. This is also advantageous as diagnostic groups will have similar IQ levels. More importantly, it enables the researcher to identify syndrome-specific differences rather than generalise the findings based on parallels in cognitive profiles. However this method may not adequately explore the research paradigm under investigation because of the differing strengths and weaknesses of each disorder. For example, a study investigating verbal and non-verbal paradigms in WS and DS would expect to observe a dissociation in these domains due to their known respective cognitive profiles, thus not be informative as to the specific areas of relative ability and impairment (Jarrold, Baddeley, & Hewes, 1999). This can be overcome with statistical techniques, such as an analysis of covariance (ANCOVA). However this also leads to a final caveat of this section regarding sample size. Due to the rarity of developmental disorders, recruitment is often problematic for logistical and financial reasons. Thus many studies present data from small samples, which then raises issues with statistical power and generalisation of the results to the population under investigation.

1.3.3 EEG / ERP methodologies

Whilst the benefits and limitations of different imaging methodologies such as fMRI / PET / functional near-infrared spectroscopy (fNIRS) are discussed widely in the literature, this final section will focus predominantly on EEG / ERP techniques as these are relevant to the thesis. Compared to some other neuroimaging techniques, ERP is non-invasive and does not require participants to be confined within a small space as is required during MRI / fMRI research.

This can be problematic for a population such as WS who experience high levels of anxiety and sensitivity to loud noises. However, ERP research does require the participant to wear a cap fitted with a chin strap, so is not without potential problems for this group with heightened sensory issues.

The literature employing ERP methodology is highly informative with regard to neural processes in typical development and developmental disorders. Several developmental disorders present ERP profiles that are independent of the level of intellectual functioning (e.g. ASD, Key & Corbett, 2014; DS, Key & Dykens, 2014; WS, Key & Dykens, 2015), thus data from this methodology should avoid the problems of controlling for mental-age matching, as raised earlier in this section. However, as highlighted in the previous section there are inconsistencies in the ERP profile possibly reflecting the recruitment of less impaired / spared cortical and subcortical regions in order to achieve the same behavioural result (e.g. ADHD, Prox et al., 2007; FXS, Menon, Leroux, White, & Reiss, 2004). Of note, data from studies using ERP paradigms have also contradicted the behavioural profile (e.g. Key & Dykens, 2015). However, this may be due to methodological differences. Behavioural paradigms in developmental disorder research most commonly require the participant to make a response (active). Due the nature of neuro-imaging methodologies, research paradigms with developmental disorders frequenty adopt passive paradigms whereby the participant is only required to observe the stimuli (e.g. Key & Dykens, 2014). Therefore, contradictions between behavioural and ERP profiles may reflect different ERP signatures between active and passive viewing. Individuals with DS also fail to discriminate at the neural level between active and passive viewing,

whereas TD controls' neural signatures differ between the two conditions (Van Hoogmoed, Nadel, Spanò, & Edgin, 2016). Thus, research which implements either passive or active recognition paradigms needs to consider the role of these different methodologies on both the ERP and behavioural profile, especially as it is also possible that passive viewing may not activate the whole memory network in developmental disorders.

1.3.4 Developmental neuronal maturation – issues of MA matching

A final methodological consideration refers back to the appropriateness of MA matching when adopting neuroimaging paradigms with adults with developmental disorders. Children's brains are still developing, whereas adults with developmental disorders have reached a stage of developed neuronal maturation, but function atypically (Karmiloff-Smith, 2013). In TD children there is maturation in both the EEG and ERP profiles from infancy up to adolescence. Slow wave activity (delta / theta) are dominant in early years, and subsequently replaced with fast frequencies (alpha / beta) with increasing age (Clarke, Barry, McCarthy, & Selikowitz, 2001), whilst gamma emerges during early childhood and matures until early adulthood (Uhlhass, Roux, Rodriguez, Rotarska-Jagiela, & Singer, 2010). Thus, investigations of alpha activity may actually record TD children's theta activity. There are also developmental differences in topographical distribution, with maturation occurring earlier at midline compared to the hemispheres and occurring last frontally across all frequencies (Gasser, Jennen-Steinmetz, Sroka, Verleger, & Möcks, 1988). Also, gender differences need to be considered, as less theta and more alpha is observed in boys compared with girls (Clarke et al., 2001). In ADHD, different maturational profiles

differ between sub-groups, but this is only in observed boys (Dupuy, Barry, Clarke, McCarthy, & Selikowitz, 2013). Thus comparisons of the EEG profiles in children with WS to those of children with ADHD may be compromised where gender and sub-group differences are not also considered.

With regard to development of ERPs, the automatic processes identified by the P3a mature earlier than controlled processes indexed by the P3b (Stige, Fjell, Smith, Lindgren, & Walhovd, 2007). Thus, when considering latency windows during data processing, it is possible that TD children's P3a is captured as their P3b in error due to the delayed latency, whilst their P3b is considered a late parietal component. These differences may also reflect the paradigm adopted, thus this issue needs to be considered based on the individual study rather than generalised to all research.

1.4 Summary

This chapter has provided an overview of core features of the developmental disorder of WS and have focused on cognition and executive function in the syndrome, providing evidence from behavioural and neuroimaging methodologies. This coverage of the literature is essential for the forthcoming empirical focus of the thesis. The following empirical chapters of the thesis will investigate claims of premature cognitive ageing in older adults with WS employing an AM paradigm (Chapter 2), and how adults with WS may use semantic memory to support encoding during an episodic memory task (Chapter 3). Chapters 4, 5, and 6 focus on how atypicalities in Chapters 2 and 3 are sub-

served by dysfunction in the executive processes of attention and inhibition, using behavioural (Chapter 4) and ERP / EEG methodologies (Chapters 5 & 6 respectively). The General Discussion (Chapter 7) will sum up the results from the five empirical chapters, linking these with key issues in the literature discussed in this chapter and the empirical chapters. The experimental work from the thesis will be used to advance our theoretical knowledge as well as emphasising new directions for research based on these findings.

Section A: Behavioural phase of the thesis

Chapter 2: Study 1 – Associative Memory

2.1 Introduction

As outlined in the General Introduction to the thesis, there is a wealth of literature investigating the cognitive abilities of younger people with WS, but relatively little is known about the age-related changes in the cognitive profile of adults with WS. To date, research has mainly concentrated on children and younger adults with WS (e.g. Bellugi et al., 2000; Edgin et al., 2010; Farran, Jarrold, & Gathercole, 2003); in comparison, the research investigating cognition in an older WS cohort is limited. Whilst the research indicates there are age-associated improvements in the cognitive abilities in individuals with WS (Jarrold et al., 2001; Porter & Dodd, 2011), the focus on development from childhood to adulthood means the age ranges of the participants are relatively young. As such these studies do not provide any information relating to age-associated changes in cognitive development in older adults with WS. In contrast, as outlined in the General Introduction (*section 1.1.5*), there is an abundance of literature documenting cognitive ageing in typically developing adults, with changes in memory functioning very much domain-specific. For example, Nyberg et al. (2003) observed a decline in episodic memory from middle- (mean age 40yrs) to older age (mean age 75yrs), in both verbal and visual paradigms. In contrast they

found age-associated improvements in performance on semantic memory tasks, adopting verbal knowledge and fluency paradigms, in adults aged up to 65 years; though they found this to subsequently decline with advancing age (>65yrs). Therefore it is highly likely that in typical development there are differential age effects on these memory skills.

With regard to cognitive ageing in WS, the results from two pivotal studies outlined in the General Introduction chapter (*section 1.1.4*) have provided the first putative evidence of a premature decline in episodic memory processes in the syndrome. The first, by Devenny et al. (2004), compared episodic memory performance, incorporating visual cued / free-recall paradigms, between young and older adults with WS (aged ≤49yrs and ≥50yrs, n=15 in each group) with individuals of similar age / IQ and with various unspecified forms of intellectual difficulty (ID) (n=33). There was an effect of level of learning difficulty and age in the free-recall task; the younger WS group recalled significantly more items than the younger ID group, which was unexpected due to poorer non-verbal ability associated with WS (Bellugi et al., 1999). However, regression analysis on the data from the free-recall task found the decline in performance by individuals with WS occurred at a chronologically earlier age than the ID group; though this must be addressed with caution due to the small sample size. More importantly, the rate of decline was steeper compared with the ID group, whose performance did not differ with age. This indicates that the decline in episodic tasks by adults with WS may have an age-associated element, and provides the first putative indication that premature cognitive ageing is a feature of the syndrome.

The second key study also identified a decline in episodic memory at a chronologically early age in adults with WS (Krinsky-McHale et al., 2005). The authors compared episodic memory performance, incorporating an oral list-learning paradigm, between a group of older adults with WS (mean age 49yrs, n=12), a group with unspecified learning difficulties (LD) (mean age 53yrs, n=39), and with adults with DS (mean age 44yrs, n=34). There was a significant age-associated reduction in performance by individuals with WS and DS. The number of items recalled from the list-learning task decreased with increasing age in both the WS and DS groups compared with the LD group who showed no age-associated decline in performance. Verbal ability is a relative strength in WS and a relative weakness in DS. As the performance by individuals with WS was comparable with the DS group, this suggests that a) adults with WS are impaired on more demanding episodic tasks which require conscious retrieval of learned information, and b) they show premature cognitive decline in a domain which is widely described as a relative strength (Bellugi et al., 2000). The studies by Devenny et al. (2004) and Krinsky-McHale et al. (2005) present the first empirical evidence supporting the suggestion of accelerated cognitive ageing in WS. The current study aims to further investigate whether memory processes associated with cognitive decline during older age in a typically developing population occur in WS and indeed whether they occur chronologically earlier in the disorder than might be predicted from typical ageing.

Section 1.1.6 of the General Introduction highlighted how AM, a type of episodic memory, is specifically affected by the typical ageing processes; whereby older adults show greater deficits in creating and retrieving associations

between single units of information (Naveh-Benjamin et al., 2003). The retrieval of associated information requires the recollection of items of information that relate to a specific event; in contrast retrieval of a single item from memory does not necessarily require the recollection of contextual information and can be the result of a familiarity judgement (Toth & Parks, 2006). An age-associated decline in AM and relatively spared recall for single items has been widely documented in the typical ageing literature. A meta-analysis by Old and Naveh-Benjamin (2008) evaluated ninety studies which included younger (mean age 21yrs, n=3,197) and older adults (mean age 71yrs, n=3,192). They found that older adults were more deficient in AM tasks than on item recognition compared with younger adults. Furthermore, AM performance in older adults is enhanced with the use of strategies, such as priming, at encoding and retrieval (Klib & Naveh-Benjamin, 2011; Naveh-Benjamin et al., 2007). However, the consistently impaired AM ability in older adults indicates that they also have problems implementing intentional associative encoding and recognition strategies (Prull et al., 2006).

There is also evidence for impaired familiarity recognition in older TD adults. For example, Jäger, Mecklinger, and Kliegel (2010) investigated whether older adults demonstrated disrupted memory for associations. They compared the performance of younger adults (mean age 24yrs) and older adults (mean age 66yrs; both groups n=20) on a face pairs paradigm incorporating intra- and inter-item associations. For the inter-item association (recollection), the two faces were physically and characteristically different. For the intra-item association (familiarity) the faces in each pair were physically different but had highly similar

characteristics, and therefore could be perceived as the same person. The authors found the younger adults were significantly better at inter-item recollection than the older adults when discriminating between the two characteristically different faces. Furthermore, the younger adults were three times better in discriminating between the similar faces compared with the older adults. In contrast, older adults were disproportionally impaired on intra-item familiarity judgements, suggesting that familiarity is not necessarily spared by the cognitive ageing process. However Jäger et al. (2010) did caution that their findings may be due to deficits in forming or encoding intra-item associations. The older adults may have been unable to unitise the two images into a single representation, rather than have impairments when making familiarity judgements. Age-associated familiarity deficits have been noted elsewhere (Li, Morcom, & Rugg, 2004), whilst a review of the research has identified inconsistent results on the stability of familiarity depending on the methodology adopted (for a discussion, see Light, Prull, LaVoie, & Healy, 2000).

Despite the limited research investigating AM ability in WS, the available research suggests this may be deficient in adults with WS (Clahsen & Almazan, 1998; Vicari et al., 2005) and DS (Carlesimo et al., 1997). Jarrold, Phillips, & Baddeley (2007) compared binding deficits in individuals with WS (aged 9yrs 1mth – 30yrs 7mths) with individuals with unspecified moderate learning difficulties (MLD) (aged 8yrs 6mths – 11yrs 7mths) and a cohort of typically developing (TD) children (aged 5yrs 10mths – 7yrs 9mths). The two control groups were matched with the WS group for non-verbal ability. The study implemented item and location memory (STM) and item-in-location (binding)

span task paradigms. There were no differences between the three groups in their total number of correct scores on item and location memory. However, both the WS and MLD groups' performance was significantly poorer on binding tasks compared with the TD group. This was supported in a study comparing a WS group (mean age 21yrs) with a MA matched control group and incorporated visual and verbal associative recognition paradigms (Costanzo et al., 2013). They also found no difference in the accuracy on item recognition between the WS and MA groups in either domain. However the WS group displayed significantly poorer accuracy on associative recognition in both the verbal and visual tasks compared with the MA group.

Notably, these studies only highlight problems of binding in WS and other forms of learning difficulties compared with age-matched typically developing control groups, and provide no evidence for an age-associated decline in AM in WS. Other authors have failed to find any difference in the binding performance between WS and MLD, and furthermore the AM deficits were evident from a relatively young age (Jarrold, Phillips, & Baddeley, 2007). Therefore, the impairments observed in individuals with WS and those with MLD when performing AM tasks suggests that deficient AM may be a factor of learning difficulties in general. However, due to the gaps in the WS literature, it is important to investigate this further in conjunction with the suggestion of premature cognitive ageing in WS.

To date, there is no known published literature that specifically addresses age-associated changes in AM in an older WS cohort. The aim of the current

study was to bridge this gap by investigating AM performance in older adults with WS, and identify whether performance declines at a chronologically earlier age than in TD adults. The study adopted item and paired-associates recognition paradigms based on the work of Naveh-Benjamin et al. (2003), and compared AM performance across verbal and visual domains. By investigating performance across these domains, it was possible to identify whether observed AM deficits in adults with WS follow not only those described in typically ageing literature, but also how performance on these tasks fit in with the known cognitive profile of the disorder. The study included a group of adults with WS aged 35yrs+ (WS), chronologically age- and gender matched typically developing individuals (CA), and a group of older typically developing adults aged 65yrs+ (65s). A general cognitive profile of adults with WS was also established to characterise this sample (e.g. the profile of skills across domains of cognition) and provide data that can be related to their performance on the AM tasks.

In the AM battery it was predicted that the WS group's performance on item recognition would be relatively spared, whereas associative recognition would be impaired, consistent with the research of Costanzo et al. (2013). However, overall performance would be impaired compared to the typical control groups due to the learning difficulties associated with WS, though impairments are hypothesised to be more distinct between the WS and CA groups. This is expected to reflect the binding problems observed in WS and decline in AM ability in the typical ageing process.

2.2 Method

2.2.1 Participants

Three groups made up the sample for this study: 1) adults with Williams syndrome (WS) aged 35+ years; 2) typically developing adults matched for gender and chronological age (CA); and 3) typically developing older adults aged 65+ years (65s). The WS group comprised of twenty adults aged 36–61 years (mean 42yrs 3mths, SD 5yrs 6mths) recruited from members of the Williams Syndrome Foundation UK. Thirteen were confirmed *FISH*-test positive and seven were diagnosed based on their clinical phenotype prior to the implementation of routine genetic testing. Thirteen participants lived with their parents in the family home, six lived in sheltered accommodation with state-provided care, and one participant lived independently. Seven participants were in some form of employment (supermarket and office workers / charity shop attendant / assist in voluntary organisations) and thirteen attended daycare centres or received state-proved care.

The CA group comprised of twenty typically developing adults aged 35–61 years (mean 42yrs 7mths**,** SD 6yrs 3mths), recruited through contacts known to the research team and via advertising within the university. The CA participants were individually age-matched within 7 months where possible to individuals in the WS group. The 65s group comprised of twenty older adults aged 67–83 years (mean 74yrs 8mths, SD 5yrs 3mths), recruited from an existing database of older adults held at Northumbria University and through local older adult groups within the Newcastle area. Each participant in the two typical control groups received £9.00 for their participation. This study received ethical clearance from the

Psychology department ethics committee at Northumbria University and approval from the advisory panel of the Williams Syndrome Foundation UK.

2.2.2 Materials

All computerised tasks were presented using a Toshiba laptop with a 12" screen. Participants were seated approximately 60cm away from the screen. All tasks were programmed using Eprime v2.00 (Schneider, Eschman, & Zuccolotto, 2001), except for the Simple Reaction Time and Spatial Working Memory tasks which were programmed with Visual Basic v6.00. An Olympus VN-4100 Digital Voice Recorder was used to record the session. A4 laminated copies of examples of all the stimuli were used as visual aids for all participants. The WS group were administered the Weschler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) in order to characterise the sample with a standardised measure of verbal and performance scores alongside a bespoke battery which provided a general cognitive profile of the participants.

2.2.3 Procedure

Two testing sessions with the WS group took place in their homes, with a parent / carer present either at the session or nearby. The control groups only required one session, which took place in the Psychology department at Northumbria University or in their own homes. Participants were greeted and seated in a comfortable chair in front of the computer screen. A verbal outline of the session was provided and participants were given the opportunity to ask questions. All participants were made aware that there would be plenty of rest breaks during the session, and that they could request a rest break at any time.

The participants from the CA and 65s groups provided written consent prior to the testing session. The parents / carers provided written consent for the WS group, and where possible written consent was provided by the WS participants. All participants gave verbal consent for the session to be tape recorded. Duration to complete the experimental procedures was approximately 1 hour 30 minutes for session one (WS, CA, 65s), and approximately 1 hour for session two for the WS group to complete the WASI. Three participants from the WS group did not complete the WASI due to illness / unavailability. Five of the WS group were unable to comply with the task demands of the verbal AM task.

2.2.3.1 General cognitive profile

A general cognitive profile of all participants was obtained through a battery of six tasks investigating reaction time, episodic memory, numeric and spatial working memory. All tasks were presented in the order outlined below, with instructions provided immediately prior to each task.

2.2.3.2 Immediate verbal recall

Twenty English words (span of 4–7 letters) were selected, taken from the Kucera-Francis lexicon for regularity. Each item was presented on screen sequentially and in a randomised order. Stimulus duration for each item was three seconds with no inter-stimulus interval. Immediately post-presentation of the complete list, participants were asked to verbally recall as many words as possible. The maximum time for recall was one minute. All participants performed a practice session prior to the experimental session to ensure they were familiar with the procedure.

2.2.3.3 Simple reaction time

Participants were presented with a blank screen. At irregular intervals the word ‘YES’ was displayed on screen; the inter-stimulus delay ranged between 1–4 seconds. The participants were required to respond as quickly as possible to the stimulus by pressing the ‘Y’ key on the keyboard. Task duration was one minute.

2.2.3.4 Spatial working memory

The participants were required to recall the location of blocked out squares presented in a grid formation. A 4-square grid was displayed on screen, two of which were blocked out. The array remained on screen for two seconds and participants were asked to remember the location of the blocked out squares. After a 2-second delay, a blank 4-square test grid was presented and participants had to indicate the location of the blocked out squares by manually pointing to their choice. The responses were recorded by the experimenter who highlighted the squares indicated by the participant using the mouse and clicking an on-screen ‘record result’ button. Correct identification of one array at level one enabled participants to advance to level two (6-square grid with three blocked out) and to the subsequent levels, each increasing in task difficulty. The maximum span was fifteen target squares in a 30-square grid. There was always an equal number of clear and blocked out squares in each array. The task ended when participants failed to correctly identify any of the three arrays in a level.

2.2.3.5 Numeric forward working memory

This task required participants to recall numeric sequences, which increased in length and task difficulty. To start, a two-digit sequence was presented sequentially on screen. Each number in the sequence remained on screen for one second, and was immediately followed by the next number with no inter-stimulus interval. To follow, an on-screen prompt asked the participants to recall the sequence out loud and in order of presentation. There were three numeric sequences in each level and participants had to recall one sequence correctly to advance to the next level. The maximum sequence length was eight digits. Participants received a practice session and the task ended when participants failed to correctly identify any of the three numeric sequences in a level.

2.2.3.6 Numeric backward working memory

This task followed the same procedure as per the Numeric Forward Working Memory task, but here participants had to recall the numeric sequence in reverse order to presentation.

2.2.3.7 Delayed recall

Participants were asked to recall out loud as many of the words presented in the Immediate Recall task as possible (40mins post encoding). The maximum time duration provided for recall was one minute.

2.2.3.8 National Adult Reading Test (NART)

The NART (Nelson, 1982) is used as an indicator of premorbid IQ. This task consists of fifty English words that follow an irregular grapheme-phoneme pattern. Participants had to read all of the words out loud and were scored for correct pronunciation. Because of the different reading abilities of the WS cohort, they received a practice list of six high frequency words to instil confidence. There was no time limit set, however the task was ceased at the experimenter's discretion if any of the WS participants struggled with the task and continuation would cause anxiety. Where this task was discontinued, any correctly pronounced words were discounted from the data analysis, due to non-completion of the full stimuli set.

2.2.4 Associative memory battery

The associative memory (AM) battery consisted of two tasks measuring performance in the verbal and visual domains. The tasks were adapted from Naveh-Benjamin et al. (2003), and the order of presentation was counterbalanced across participants. See Appendices *i* (verbal) and *ii* (visual) for full details of all stimuli.

2.2.4.1 Verbal associative memory

The stimuli consisted of sixty English words taken from the University of Western Australia database using familiarity, imagery, and concreteness as criteria. Word span ranged between 4–7 letters. The stimuli were divided into thirty semantically related and thirty semantically unrelated word pairs. Verification of relatedness was conducted with a pilot study. Ten participants who

did not take part in the current study were asked to rate word pairs for semantic relatedness on a scale of 1–10. Semantically related pairs scored eight and above, whilst semantically unrelated pairs scored two and below. There were ten semantic categories with three word pairs in each. Participants were instructed they would see a series of word pairs presented on screen (Arial font size 24). They were to concentrate on both the word pair and any association between the words. Each pair was presented in a fully randomised order for four seconds and with an inter-stimulus interval of 250ms during which a fixation point was displayed. All participants received a practice session. Post-presentation the participants conducted item and associative memory forced choice recognition tasks.

2.2.4.2 Item recognition

Twenty-four word pairs were presented in a randomised order, each for five seconds. One word in each pair was from the original study list and the other was a new item. Participants had to identify which word they had previously seen, by pressing the 'C' key with their left index finger for the word on the left, or the 'M' key with their index finger for the word on the right. Participants were asked to respond as quickly and accurately as possible.

2.2.4.3 Associative memory recognition – paired-associates

Forty-eight word pairs were displayed on screen in a randomised order. Maximum on-screen duration for each pair was five seconds, followed by an inter-stimulus interval of 250ms during which a fixation cross was displayed. Participants had to state whether they had seen the pair previously or not with a

forced choice ‘YES / NO’ response using designated keys on the keyboard. Twenty-four pairs were intact and had been shown during the study phase, and twenty-four pairs were new pairings rearranged from the study pairings. In the related condition, the pairs were rearranged within the same semantic category. There was no duplication of words included in the intact and rearranged pairs.

2.2.4.4 Visual AM

The stimuli consisted of thirty-six picture pairs which were semantically unrelated. Verification of relatedness was conducted as per the verbal AM task, with only the pairs scoring two or below included in the final stimuli set. At study, the picture pairs were presented in a randomised order on screen for four seconds. This was interspersed by a one-second inter-stimulus interval during which a fixation cross was displayed. Participants were instructed to try and remember each pair. Post-presentation participants completed item and associative memory recognition tests. All participants received a practice session.

2.2.4.5 Item recognition

Twenty-four single images were presented sequentially on screen and in randomised order, each for a maximum of five seconds. Twelve items were from the original list and twelve items were new. A forced choice paradigm was incorporated whereby participants had to state whether each image was from the original list or not by pressing designated ‘YES’ / ‘NO’ keys on the keyboard.

2.2.4.6 Associative memory recognition – paired-associates

The stimuli consisted of twenty-four picture pairs, twelve pairs intact from the study phase and twelve rearranged pairs. In the rearranged condition, one item from each pair was replaced by an item from a different pair but contained equally plausible characteristics to the original. For example, a chair was replaced with a bench (see Appendix *ii*). Participants were required to identify whether they had seen each pair in the original list, with the same procedure as in the verbal AM task.

2.3 Results

2.3.1 WASI

The mean FSIQ score was 60.89 (SD 6.60). Analysis of the subtests revealed scores on Verbal IQ (mean = 62.29, SD 7.53) were significantly lower than Performance IQ (mean = 66.18, SD 9.92) [t(16) = –2.615, p=.019].

2.3.2 General cognitive battery

All data from the general cognitive battery were analysed with a one-way analysis of variance (ANOVA). Means and standard deviations (SD) for all tasks are presented in Table 1.

2.3.2.1 Immediate memory

There was a significant effect of group on immediate word recall [F(2,56) = 20.656, p<.001]. The WS group recalled significantly fewer words than both the

CA group (p<.001) and the 65s group (p=.001). The CA group recalled significantly more words than the 65s group (p=.042).

2.3.2.2 Delayed recall

There was a significant effect of group on delayed word recall [F(2,55) = 12.625, p<.001]. The WS group recalled significantly fewer words than both the CA group (p<.001) and the 65s group (p=.017).

2.3.2.3 Simple reaction time

There was a significant effect of group on simple reaction time [F(2,59) = 18.628, p<.001]. The WS group's RT was significantly slower than both the CA and the 65s groups' (both p<.001), whereas there was no difference between the CA / 65s groups' RT (p=1.00).

2.3.2.4 Spatial working memory

There was a significant effect of group on spatial working memory [F(2,59) = 62.234, p<.001]. The WS group's mean span was significantly lower than both the CA and the 65s groups' (both p<.001), whereas the CA group's mean span was significantly greater than the 65s' (p<.001).

2.3.2.5 Verbal working memory (forward)

There was a significant effect of group on forward verbal working memory [F(2,58) = 41.085, p<.001]. The WS group's maximum span was significantly lower than both the CA and 65s groups' (both p<.001). There was no difference between the CA / 65s groups (p=.409).

2.3.2.6 Verbal working memory (backward)

There was a significant effect of group on backward verbal working memory [F(2,57) = 37.246, p<.001]. The WS group's maximum span was significantly lower than both the CA and 65s groups' (both p<.001). There was no difference between the CA / 65s groups (p=.204).

2.3.2.7 National Adult Reading Test (NART)

There was a significant effect of group on the number of words correctly pronounced on the NART [F(2,55) = 82.654, p<.001]. The number of words correctly pronounced by the WS group was significantly lower than both the CA and 65s groups (both p<.001). There was no difference between the CA and 65s groups on number of words correctly pronounced (p=.153).

Table 1: Mean score on all tasks of the general cognitive battery by the WS, CA, and 65s groups. SDs in parentheses

	Imm recall words	**Del recall words**	**Simple RT Secs**	**Spatial WM span**	**NART words corr**	**Verbal WM (forward span)**	**Verbal WM (backward span)**
WS	**2.76** *(2.05)*	**1.44** *(2.03)*	**.86** *(.57)*	**3.70** *(1.34)*	**7.38** (7.97)	**3.89** *(1.05)*	**2.79** *(1.40)*
CA	**8.15** *(2.92)*	**5.90** *(3.09)*	**.28** *(.04)*	**9.30** *(1.95)*	**34.35** (6.92)	**6.75** *(1.12)*	**6.20** *(1.32)*
65s	**6.10** *(2.53)*	**4.00** *(2.60)*	**.32** *(.04)*	**6.60** *(1.31)*	**39.3** (8.57)	**6.25** *(0.97)*	**5.45** *(1.10)*

2.3.3 Verbal associative memory

A 3 x 2 repeated measures ANOVA was applied to the data with Group (WS, CA, 65s) as the between measures factor and Condition (related, unrelated) as the within measures factor.

2.3.3.1 Verbal item recognition – correct identification

Summary data are presented in Table 2. There was a significant main effect of Group [$F(2,52) = 17.498$, $p<.001$] but no main effect of Condition [$F(1,52) = .499$, $p=.483$], and no Group x Condition interaction [$F(2,52) = 1.189$, $p=.313$] on verbal item recognition.

Group: Tukey post-hoc analyses revealed significantly lower item recognition in the WS group compared with both the CA and 65s groups (both p<001). There was no difference in verbal item recognition between the CA and the 65s groups ($p=.399$).

2.3.3.2 Reaction time (RT)

There were no significant main effects of Group [$F(2,52)$, $= .801$, $p=.454$] or Condition [$F(1,52) = 1.492$, $p=.227$], and no Group x Condition interaction [$F(2,52) = 1.225$, $p =.302$] on verbal item-recognition RT.

Table 2: Percentage of correctly recalled items and RT by condition. SDs in parentheses

	Correct identification %		**Reaction time (ms)**	
	Related	Unrelated	Related	Unrelated
WS	**62.2** *(18.0)*	**60.6** *(16.55)*	**2093.98** *(839.17)*	**2155.45** *(721.13)*
CA	**82.1** *(9.86)*	**84.7** *(10.2)*	**1784.34** *(538.36)*	**1927.96** *(496.15)*
65s	**81.7** *(15.3)*	**75.8** *(15.0)*	**1956.95** *(752.64)*	**1926.86** *(559.07)*

2.3.3.3 Verbal associative memory – paired-associates

A 3 x 2 repeated measures ANOVA was applied to both the hits and false alarms (FAs), and reaction time (RT) data, with Group (WS, CA, 65s) as the between measures factor, and Condition (related, unrelated) as the within measures factor. Summary data are presented in Table 3.

Table 3: Percentage of hits and FAs, and RT in ms in the related and unrelated conditions of the verbal paired-associates task. SDs in parentheses

	Related %		**Unrelated %**		**Related RT (ms)**		**Unrelated RT (ms)**	
	Hits	FA	Hits	FA	Hits	FA	Hits	FA
WS	**62.3** *(29.1)*	**53.4** *(30.9)*	**56.7** *(29.6)*	**54.4** *(30.9)*	**1820.18** *(743.18)*	**1777.49** *(724.06)*	**1770.15** *(700.55)*	**1841.90** *(711.79)*
CA	**81.3** *(15.0)*	**29.6** *(20.7)*	**64.6** *(22.2)*	**33.0** *(14.8)*	**1717.88** *(332.10)*	**1813.17** *(811.75)*	**1833.44** *(407.87)*	**2129.53** *(563.99)*
65s	**88.9** *(11.0)*	**43.8** *(24.8)*	**62.9** *(26.3)*	**29.3** *(19.3)*	**1737.38** *(400.63)*	**1842.34** *(548.33)*	**2059.81** *(591.46)*	**2217.05** *(654.08)*

2.3.3.4 Hits

The analysis revealed significant main effects of Group [F(2,52) = 3.377, p=.042] and Condition [F(1,52) = 25.153, p<.001], and a significant Group x Condition interaction [F(2,52) = 3.179, p=.05]. See Figure 1.

Group: Tukey post-hoc comparisons identified significantly lower hit rates in the WS group compared to the 65s group (p=.042). There was no difference in the hit rates between the WS and CA groups (p=.112), and the CA and the 65s groups (p=.883).

Condition: The significant main effect of condition was due to significantly greater hits in the related condition than in the unrelated condition (p<.001).

*Group*condition:* Paired samples t-tests found no difference in the hit rates between the related and unrelated conditions in the WS group (p=.277), whereas both the CA and the 65s groups' hit rates were significantly greater in the related condition (CA, p=.08; 65s, p<.001). Independent t-tests also found a significantly lower hit rate in the WS in the related condition compared to both the CA (p=.032) and the 65s groups (p=.004). There was no difference in hit rates by Group in the unrelated condition (p≥.371).

2.3.3.5 False alarms (FAs)

The ANOVA revealed a significant main effect of Group [F(2,52) = 5.376, p=.008] but not for Condition [F(1,52) = 1.261, p=.267], and a significant Group x

Condition interaction [F(2,52) = 3.716, p=.031] on FAs in the verbal paired-associates task.

Group: Tukey post-hoc comparisons revealed a significantly greater FA rate in the WS group than both the CA (p=.007) and the 65s groups (p=.046). There was no difference in FAs between the CA and the 65s groups (p=.705).

*Group*Condition:* Paired samples t-tests revealed the 65s group made significantly more FA in the related condition than in the unrelated condition (p=.03). In contrast there was no difference by condition in FA rates in both the WS (p=.796) and the CA groups (p=.479). Independent t-tests found a significant greater FA rate in the WS group compared to the CA group (p=.01) in the related condition. There was no difference in FAs between the WS / 65s (p=.315), whilst the 65s group's numerically greater number of FAs approached significance compared to the CA group (p=.057). In the unrelated condition, the WS group made significantly more FAs compared to both the CA (p=.023) and the 65s groups (p=.006). There was no difference in FAs between the CA and 65s groups (p=.50).

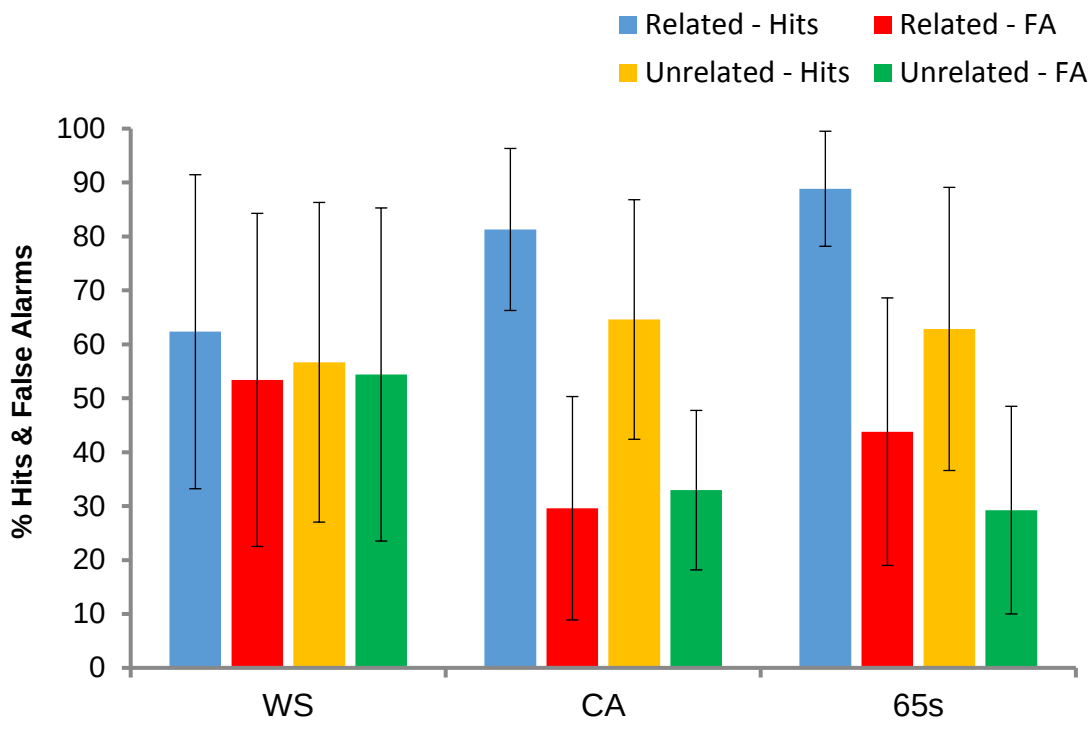


Figure 1: Mean percentage of hit and FA rates in the WS, CA, & 65s groups on the verbal paired-associates task. Error bars represent SDs

2.3.3.6 Reaction time (RT) to hits

The ANOVA revealed no significant main effect of Group [F(2,52) = .319, p=.729], a significant main effect of Condition [F(1,52) = 13.433, p<.001], and significant Group x Condition interaction [F(2,52) = 9.055, p<.001) on RT to hits.

Condition: The main effect of Condition was due to significantly faster RT in the related condition compared to the unrelated condition (p=.001).

*Group*Condition:* Paired samples t-tests revealed no difference in RT by Condition in the WS group (p=.538). In contrast both the CA and the 65s groups' RT was significantly faster in the related condition compared to the unrelated

condition (CA, p=.022; 65s, p<.001). Independent samples t-tests revealed no difference between the groups on RT in either the related or unrelated conditions (all p≥.194).

2.3.3.7 Reaction time (RT) to FAs

The ANOVA revealed no main effect of Group [F(2,52) = .633, p=.535], a significant main effect of Condition [F(1,52) = 7.789, p=.007], and a significant Group x Condition interaction on RT to FAs [F(2,52) = 1.019, p=.038].

Condition: Pairwise comparisons revealed significantly faster RT in the related condition compared to the unrelated condition (p=.007).

*Group*Condition:* Pairwise comparisons revealed no difference in RT by Condition in both the WS (p=.398) and CA groups (p=.155), whereas the 65s group's RT was significantly faster in the related condition compared to the unrelated condition (p=.003). Independent t-tests found no differences in RT to FAs between the groups in either the related or unrelated conditions (all p≥.115).

2.3.4 Visual associative memory task – item recognition

A 3 x 2 repeated measures ANOVA was applied to the data, with Group (WS, CA, 65s) as the between measures factor, and Response (hits, FAs) as the within measures factor. Siummary data are presented in Table 4.

Table 4: Percentage of hits and FAs, and RT in the visual item-recognition task. SDs in parentheses

	Response type %		**Reaction time (ms)**	
	Hits	FA	Hits	FA
WS	**71.4** *(26.1)*	**35.4** *(29.8)*	**1369.11** *(503.84)*	**1296.13** *(690.48)*
CA	**95.0** *(9.1)*	**2.5** *(4.7)*	**896.02** *(227.31)*	**351.20** *(697.95)*
65s	**89.7** *(14.0)*	**6.2** *(7.6)*	**1008.99** *(196.41)*	**722.69** *(891.53)*

2.3.4.1 Visual item recognition – response (hits cf. FAs)

There was no significant main effect of Group [$F(2,57) = .920$, $p=.404$], a significant main effect of Response [$F(1,57) = 550.016$, $p<.001$], and a significant Group x Response interaction [$F(2,57) = 33.859$, $p<.001$] on visual item recognition.

Response: Pairwise comparisons confirmed significantly greater hits to false alarms ($p<.001$).

*Group*Response:* Paired samples t-tests revealed significantly greater hit rates than FAs in all three groups (all $p<.001$). Independent samples t-tests revealed significantly greater hit rates in both the CA and the 65s groups compared with the WS group (CA, $p=.001$; 65s, $p=.01$) but no difference between the CA / 65s ($p=.164$). FA rates were significantly greater in the WS group compared to both the CA and 65s groups (both $p<.001$). There was no difference in FA rates between the CA / 65s groups ($p=.071$).

2.3.4.2 Reaction time (RT)

The ANOVA revealed significant main effects of Group [F(2,57) = 11.893, p<.001], and Response [F(1,57) = 10.290, p=.002], but no Group x Response interaction [F(2,57) = 1.979, p=.148] on visual item-recognition RT.

Group: Tukey post-hoc comparisons revealed significantly slower RT in the WS group compared with both the CA (p<.001) and the 65s groups (p=.007). There was no difference in RT between the CA and the 65s groups (p=.233).

Response: Pairwise comparisons revealed significantly faster RT to hits compared with FAs (p=.002).

2.3.5 Visual associative memory – paired associates

A 3 x 2 mixed measures ANOVA was applied to the data, with Group (WS, CA, 65s) as the between measures factor, and Response (hits, FAs) as within measures factors. Summary data are presented in Table 5.

Table 5: Percentage of hits and FA, and RT in ms in the visual paired-associates task. SDs in parentheses

	Response %		**Reaction time (ms)**	
	Hits	FA	Hits	FA
WS	**73.7** *(21.8)*	**75.8** *(21.3)*	**1350.51** *(397.01)*	**1402.47** *(483.59)*
CA	**87.5** *(15.5)*	**56.3** *(21.9)*	**1344.49** *(468.91)*	**1723.53** *(572.39)*
65s	**82.6** *(17.5)*	**75.4** *(16.8)*	**1541.30** *(460.87)*	**1656.23** *(505.85)*

2.3.5.1 Hits and FAs

The ANOVA revealed no significant main effect of Group [$F(2,57) = 1.041$, $p=.360$], a significant main effect of Response [$F(1,57) = 17.192$, $p<.001$], and a significant Group x Response interaction [$F(2,57) = 11.663$, $p<.001$] on visual AM hit and FA rates. See Figure 2.

Condition: Pairwise comparisons revealed significantly greater hits than FAs ($p<.001$).

*Group*Response:* Pairwise comparisons found significantly greater hits than FAs in the CA group ($p<.001$), whereas there was no difference between hits / FA rates observed in both the WS and the 65s groups ($p\geq.134$). Independent t-tests identified significantly greater hits in the CA group compared to the WS group ($p=.026$), whereas the WS group's FA rate was significantly greater compared to the CA group ($p=.007$). There was no difference between the WS and the 65s groups in both hits ($p=.163$) and FA ($p=.948$). There was also no difference between the CA / 65s on hit rates ($p=.349$), whereas the 65s' FA rate was significantly greater than the CA group's ($p=.004$).

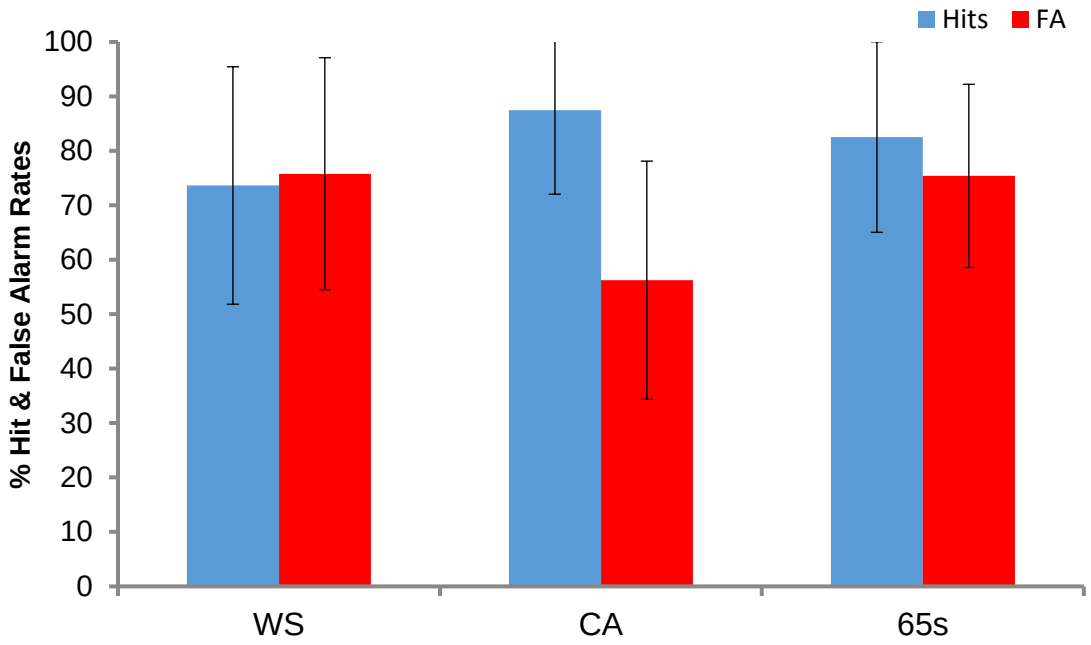


Figure 2: Mean percentage of hit and FA rates in the WS, CA, & 65s groups in the visual paired-associates task. Error bars represent SDs

2.3.5.2 Reaction time (RT)

The ANOVA revealed no main effect of Group [F(2,57) = 1.278, p=.287], a significant main effect of Response [F(1,57) = 16.576, p<.001], and a significant Group x Response interaction [F(2,57) = 5.025, p=.01] on visual AM RT. See Figure 3.

Response: Pairwise comparisons revealed significantly faster RT to hits than FAs (p<.001).

*Group*Response:* Paired samples t-tests revealed no difference in RT between hits and FA in the WS group (p=.446) and the 65s group (p=.114), whereas the CA group's RT was significantly faster in response to hits (p=.001). Independent t-tests revealed no difference between groups in RT to hits (p≥.169). RT to FA

between the WS / CA groups approached significance (p=.063), where the WS group's RT was faster than the CA group's. There was no difference in RT between the WS / 65s (p=.502) and the CA / 65s (p=.113).

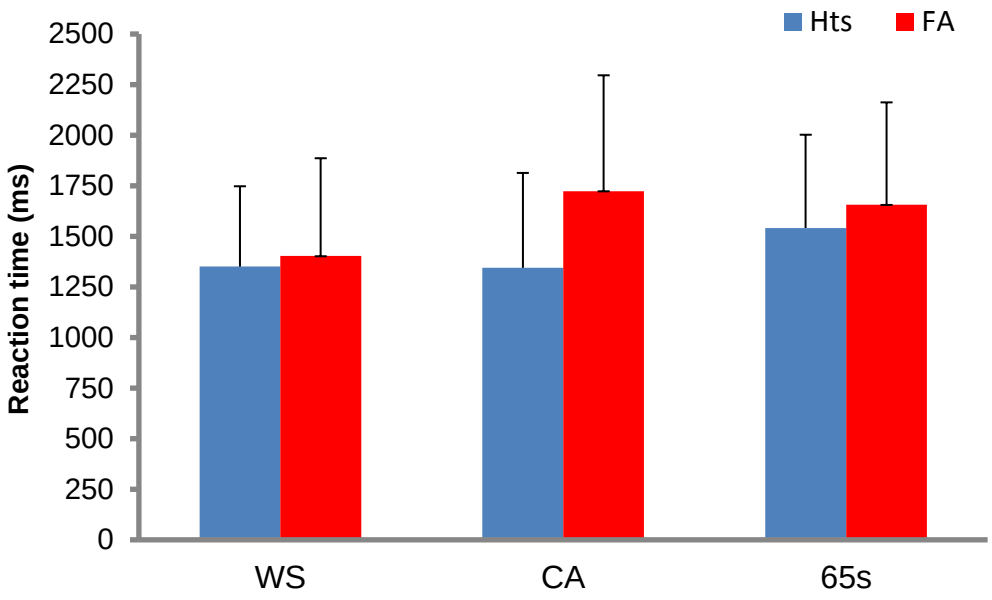


Figure 3: RT (ms) to hits and FAs for the WS WS, CA, & 65s groups in the visual paired-associates task. Error bars represent SDs

2.4 Discussion

The principal objective of the current study was to investigate whether previous claims of premature cognitive ageing in adults with WS (aged 35+yrs) could be supported by adopting an associative memory (AM) paradigm. A bespoke battery of tasks was administered to measure general cognitive performance, supplemented with standardised measures of verbal and performance IQ using the Wechsler Abbreviated Scale of Intelligence (WASI). The results found deficits in both item recognition and AM in adults with WS.

Thus, rather than finding further evidence for premature cognitive ageing (cf. Devenny et al., 2004; Krinskey-McHale et al., 2005), they support the existing literature that identifies 'binding' as problematic in WS (Jarrold, Phillips, & Baddeley, 2007; Vicari et al., 2005). Specifically, in the verbal task, the pattern of data indicates an inability of the WS group to capitalise on semantic memory during both item- and paired-associates recognition. In the visual task, the data also suggest that adults with WS were unable to implement spontaneous encoding strategies in the absence of a semantic relationship between the paired stimuli. The main findings will be presented first, followed by a critique of the study including suggestions for the subsequent studies in the thesis.

Overall the WS group's performance on verbal item recognition was poorer than both the CA and the 65s groups in both the related and unrelated conditions. This could not be accounted for as a speed–accuracy trade-off in the WS group as there was no difference in RT between groups in both conditions. Speed–accuracy trade-offs are typically evidenced by faster RT and poorer performance. Though not significant, the WS group's RT was slower than both control groups. There was a dissociation between the WS and CA groups in visual item recognition, with significantly greater hits observed in the CA and the 65s groups compared with the WS group. In contrast the WS group made significantly more FAs than both control groups. This was also not reflective of a speed–accuracy trade-off in the WS group as their RT was significantly slower than both the CA and the 65s participants. There was no difference in verbal and visual item recognition between the CA and the 65s groups, which is consistent with the literature demonstrating robustness of familiarity in typically developing older

adults (Naveh-Benjamin et al., 2003), and to be expected as the methodological paradigms employed here and by Naveh-Benjamin et al. (2003) were the same (cf. Light et al., 2000). However, the performance by the WS group on the item-recognition tasks in the current study contradict the only other known published research investigating behavioural indices of AM in WS, and which found familiarity to be spared in younger WS adults (Costanzo et al., 2013). However there are notable methodological differences between the current study and Constanzo et al. (2013). Their paradigm required the participants to make 'Yes / No' pleasantness discriminations for each stimulus, which may have enhanced encoding to a deeper level, but this was not included in the current study in either domain. This will be addressed in greater detail in the General Discussion (Chapter 7).

In the verbal paired-associates task, the WS group's hit rate was significantly lower compared to the 65s group but not the CA group, thus not supporting the poorer AM performance previously found in the younger WS cohort in the Costanzo et al. (2013) study. Therefore, this suggests the results are not indicative of premature cognitive ageing in this group; rather they provide further support for the known 'binding' deficits documented in the WS literature (e.g. Jarrold, Phillips & Baddeley, 2007; Vicari et al., 2005). Furthermore, when comparing performance between the semantically related and unrelated word pairs, the data highlighted a pattern in the WS group indicative of atypical access to semantic memory. There was no difference in WS group's hit rates and RT irrespective ofcondition. In contrast, greater hit rates and faster RT in the related condition compared with the unrelated condition was observed in both control

groups. This pattern therefore suggests that the WS group were unable to benefit from semantic memory during a verbal paired-associated task. This was supported by the FA results, where again the WS group made significantly more FAs than the CA group despite comparable RTs. In contrast, the high FA rate observed in the 65s group most likely reflects a speed–accuracy trade-off due to the significantly faster RT to FAs compared to both the WS and the CA groups. Notably, there was no difference by condition in both the hit and FA rates between the CA and the 65s groups on the verbal paired-associated task. This contradicts the widely acknowledged decline in AM in typically developing older adults (Chalfonte & Johnson, 1996; Old & Naveh-Benjamin, 2008).

In the visual paired-associates task, the WS and CA groups presented a similar dissociation as observed in the visual item-recognition task. A significantly lower hit rate and significantly greater FA rate was observed in the WS group compared with the CA group. The WS group also showed no difference in RT between the hits and FAs, whereas the CA group's RT to hits was significantly faster than their RT to FAs, emphasising discrimination at the behavioural level between the intact and rearranged picture pairs. Notably, both the WS and the 65s groups' FA rates were very high which suggests that participants in both groups were a) unable to form spontaneous encoding strategies in the absence of a semantic manipulation, or b) may have responded to the familiarity of the individual items in the pairing rather than to the association between the items. Interpretation of the results is more problematic as both groups had the same RT to FAs; however three suggestions are proposed to explain this pattern in the data. First, the results are consistent with the literature showing that the AM

deficits observed in typically developing older adults are more likely to be a result of higher FA rates rather than a decline in hit rates (Naveh-Benjamin et al., 2003, 2009). Second, an age-associated decline in the ability to form spontaneous encoding strategies has been documented in typically ageing older individuals (Kirchhoff, Anderson, Barch, & Jacoby, 2012). The comparable inability to reject the rearranged pairings by the WS and the 65s groups initially suggests that traits associated with cognitive ageing in typical development can also be associated with the WS phenotype. However, the rearranged item in each pair was visually equally plausible to the original item (e.g. a golf ball replaced with a tennis ball). Therefore, a third and more parsimonious explanation proposes that the replaced picture in each rearranged pair was too similar to the original, and both the WS and the 65s participants were unable to detect the change. This could also be reflected in the FA rate observed in the CA group which was at chance level.

When evaluating age-associated issues of AM ability in adults with WS, consideration also needs to be given to the choice of control groups (as highlighted in the General Introduction). Commonly, research with developmental disorders includes a group matched for mental age (MA). However, as the specific focus of the current study was investigation of premature cognitive ageing and based on the supporting literature which suggests that this group's AM performance is not reflective of IQ (e.g. Clahsen & Almazan, 1998; Jarrold, Phillips, & Baddeley, 2007), a mental age-matched cohort was not included. As the results did not reflect either the chronological age of the WS group, or provide evidence for premature cognitive ageing, the study would have benefited from comparison with a mental age-matched group for completeness. Furthermore,

the overall performance by the 65s group suggests that these participants were a high functioning cohort and therefore not a representative sample of typically developing older adults, as research with low-performing typically developing older adults has documented impairments on both familiarity and recollection (Duarte, Ranganath, Trujillo, & Knight, 2006).

A final consideration of this study relates to the performance on the general cognitive battery and IQ measures. The overall performance by the WS group on the general cognitive battery was poorer than both the CA and the 65s groups, with lower accuracy and slower reaction times observed in all tasks. This was expected due to the learning difficulties associated with WS (Bellugi et al., 1999). Notably, both the WS and 65s participants' performance on the working memory (WM) tasks emphasised the differences in their profiles due to atypical development / typically ageing processes. The WS group's performance was impaired compared to both TD groups as previously observed (Menghini et al., 2010; Rhodes et al., 2011). This contradicts other research which has found selective deficts of spatial but not verbal WM (e.g. Costanzo et al., 2013, Jarrold et al., 2007) indicative of an overall WM deficit in this group of WS individuals. In contrast the 65s group reported a domain specific profile with comparable performance to the CA group in both verbal WM tasks, but impaired performance on the spatial WM task. Again, this is consistent with the literature which emphasises age-associated impairments in spatial WM in older TD adults (Bopp & Verhaegen, 2007). The National Adult Reading Test (NART) was included in the study as a premorbid predictor of IQ (Nelson, 1982), and has been used previously in clinical settings and in research with individuals with learning

difficulties (e.g. McCabe, Hillier, & Shapiro, 2012; Willis, Palermo, Burke, McGrillen, & Miller, 2010). However, it was apparent that the reading ability of the adults with WS recruited for this study had been overestimated. Overall, the WS group had great difficulty pronouncing the words evidenced by the very low number of responses, which suggests that the NART is not an appropriate measure of IQ in this group. The mean score from the WASI was consistent with the full-scale IQ scores typically associated with WS (Martens et al., 2008); whereas an inverse pattern was observed in the subtests scores, with greater performance IQ scores and lower verbal IQ. However, inspection of the data at individual level by subtest found better or equal verbal IQ compared with performance IQ, and has been previously noted in the literature (Farran et al., 2010; Howlin et al., 1998; also see Porter & Coltheart, 2005 for a discussion). This emphasises issues regarding the use of standardised tests as discussed in Chapter 1.

In summary, the current study found no evidence for premature cognitive ageing in older adults with WS, linking to the literature that was covered in the General Introduction chapter. The data showed an inability to capitalise on semantic memory in the verbal domain, and the inability to form spontaneous semantic encoding strategies in the absence of a semantic manipulation in the visual domain for adults with WS. Chapter 3 will address these deficits by focusing on the role of semantic memory during the encoding phase of a memory paradigm.

Chapter 3: Study 2 – Levels of Processing

3.1 Introduction

The results from Chapter 2 highlighted deficits in adults with WS in capitalising on semantic memory, and the inability to form spontaneous semantic encoding strategies during episodic memory tasks. *Section 1.1.8* of the General Introduction outlined the role of semantic cognition in WS, with more and less proficient areas of functioning; for example unusual and low frequency exemplars in semantic fluency tasks (e.g. Bellugi et al., 1994), relatively spared access to semantic memory (Tyler et al., 1997), and impairments in the monitoring of responses (Jarrold et al., 2000). The latter indicates that the atypicalities associated with performance on this type of semantic task are not linked solely to memory or language skill but are also grounded in atypical executive processes. In TD individuals, fMRI research has highlighted greater BOLD activation in the DLPFC during semantic interference, indicative of greater recruitment of these inhibitory processes (Hoenig & Scheef, 2009). In WS, atypical activity in frontal regions including the DLPFC is documented, and linked with their deficits in inhibitory processing (Mobbs, Eckert, Mills et al., 2007).

As demonstrated in Chapter 2, when LTM requires the encoding or retrieval of rich item and contextual information, difficulties are observed for individuals with WS. However, similar to the pattern observed in the typically ageing process, research shows this is accompanied by relatively less difficulty

with memory for more automatic, overlearned information involving semantic memory (Lee & Binder, 2014). Therefore, in light of the difficulties adults with WS found capitalising on semantic memory in Chapter 2, the focus of Chapter 3 considered whether adults with WS could benefit from semantic support during encoding during a LTM task. Given the relative proficiency of semantic memory skills, Chapter 3 investigated whether adults with WS were able to use semantic memory as a strategy to support more evident deficits of episodic memory processing.

One method of investigating the role of semantic processing during memory tasks is by adopting the Levels-of-Processing paradigm (LoP; Craik & Lockhart, 1972). In TD individuals, shallow processing (e.g. focusing on perceptual / phonological components of the stimuli) leads to a fragile memory trace as the information is less embedded in semantic memory, resulting in relatively poor subsequent recall. In contrast, deep processing (e.g. making semantically related decisions about the stimuli) results in a more durable memory trace and typically relatively superior recall (Craik & Lockhart, 1972). In typical development, individuals benefit from LoP across the lifespan (Luo, Hendriks, & Craik, 2007; Troyer, Häfliger, Cadieux, & Craik, 2006), and it can facilitate memory improvement in older age when memory processes such as episodic memory are known to decline (Grady & Craik, 2000).

There has been a dearth of research exploring the way that episodic memory and semantic memory interact in WS. The only known study which has compared phonological (shallow) compared with semantic (deep) encoding in

WS found no difference between conditions in recall on a verbal STM task (Laing et al., 2005). However, as STM is relatively impaired in WS (Vicari et al., 2003), this may outweigh any benefit for deeper encoding on item recall. Similar research adopting a LoP paradigm in other developmental disorders is also limited. In the one known study that has taken a LoP approach to memory in ASD, Toichi and Kamio (2002) failed to demonstrate a benefit of deeper processing in their participants with ASD. Rather, they had superior episodic memory performance when using less efficient perceptual and rote encoding strategies, and is very different to the pattern observed in typical development. Therefore, while it is possible that this is a pattern of memory performance specific to ASD, it could be a characteristic of general intellectual difficulty.

The aim of the current study was therefore to extend investigations of the LoP paradigm to adults with WS (aged 35+yrs) and elucidate whether this provides a supportive role to the deficient semantic memory and spontaneous semantic encoding strategies described in Chapter 2. Two control groups were included: a group of TD adults matched for chronological age (CA), and a group of TD children matched for verbal mental ability (MA). It was hypothesised that 1) all groups would have better recall for items encoded with deep rather than shallow processing, and 2) the WS group would present an overall impairment in task performance, indexed by lower recall and increased RT compared to both control groups.

3.2 Method

3.2.1 Participants

A group of 20 adults with WS (35–63 years, mean 43yrs 2mths) was matched to two typically developing comparison groups on chronological age and gender (CA, n=20; 35–63yrs, mean 43yrs 9mths)**,** and verbal mental age and gender (MA, n=20; 5–14yrs, mean 9yrs 8mths). Verbal MA was measured using the British Picture Vocabulary Scale (BPVS II; Dunn, Dunn, Whetton, & Burley, 1997); see Table 6 for group demographics. The adults with WS were recruited via the Williams Syndrome Foundation UK.

Fifteen individuals with WS had previously had their clinical diagnosis confirmed with fluorescent in situ hybridisation (*FISH*) testing to detect the deletion of one copy of the elastin gene on chromosome 7. The remaining five individuals had a clinical diagnosis, but this took place prior to the implementation of routine genetic testing. Three lived independently and seventeen lived at home with their parents / carers or in sheltered accommodation. Six were in some form of employment (supermarket and office workers / charity shop attendant / help in voluntary organisations) while the rest attended daycare centres or receive state-proved care assistance. The participants in the two typical comparison groups received £6.00 for their participation. This study was approved by the ethics committee, Department of Psychology, Northumbria University.

Table 6: Demographic details for the WS, CA, & MA groups

	WS	**CA**	**MA**
n	20	20	20
Age range	35–63 yrs	35–63 yrs	5–14 yrs
Mean age *(SD)*	43:2 *(6:7)*	43:9 *(6:6)*	9:8 *(2:4)*
Mean BPVS score	105.00 *(17.37)*	n/a	105.40
Vocabulary age	10:9 *(3:7)*	n/a	11:04 *(2:7)*

Years:months; standard deviations *(SD)* in parentheses

3.2.2 Materials & design

Forty-eight colour pictures from six semantic categories (animals, clothing, fruit, tools, toys, & vehicles) were taken from the Snodgrass and Vanderwart (1980) set, and matched for concept and frequency. Twenty-four images made up the stimuli for the shallow processing condition and twenty-four were selected for the deep processing stimuli. Each condition contained four exemplars of each of the six semantic categories and no item was duplicated across the conditions. In the shallow condition, half of the images were framed with a black border, and half were unframed (providing a perceptual-level difference). A further twenty-four images (four from each semantic category), not included in the encoding stimuli set, were selected for the new items presented during the test phase.

The task was programmed using Eprime v2.00 (Schneider et al., 2001) and stimuli were presented on a Toshiba laptop with a 12” screen. A4 laminated examples of the stimuli (not included in the experimental stimuli set) were used as visual aids for all participants during explanation of the task. See Appendix *iii* for a breakdown of item / category / condition allocation.

3.2.3 Procedure

Testing sessions for participants with WS took place in their homes, with a parent / carer present or nearby. Testing for the typical comparison groups took place in the Psychology department at Northumbria University. To commence the session, the participants were greeted by the experimenter and seated in a comfortable chair in front of the computer. The experimenter outlined the experimental procedure, using the A4 laminate sheets to aid explanation, and invited each participant to read and sign an informed consent form. Where certain individuals from the WS group did not have sufficient reading ability, their parent / carer read the information sheet out loud. Written informed assent was provided by the adults with WS where possible and was always in addition to consent provided by the individual's parent / carer.

During the encoding phase, participants were presented with the forty-eight stimuli, one at a time on a computer screen. Each item was preceded with a ***'?'*** in Arial font size 28, displayed on screen for five seconds. During this time the experimenter asked an encoding question which was presented in either shallow or deep processing format. The shallow encoding question was always *'Is the next item in a frame?'* thus focusing on perceptual features of the item. The deep encoding questions always focused on the item's semantic category membership, e.g. *'Is the next item something a workman would use / a type of fruit / something you would play with?'* All questions required a verbal YES / NO response which was recorded manually by the experimenter. Half of the responses in each condition were 'YES' and half were 'NO'. Each item remained

on screen for three seconds and was followed by a blank inter-stimulus interval of 250ms. The order of presentation was pseudorandomised to ensure that no two images from the same semantic category were presented sequentially, irrespective of whether they were accompanied with shallow or deep encoding instructions. The first two and last two stimuli in the list acted as buffers and were not included in the test stimuli.

Immediately after the study phase, participants were presented with on-screen instructions advising they would be shown a further series of images one at a time and they were to identify whether they had seen each previously or not, by pressing designated YES / NO keys on the keyboard. The experimenter verbalised these instructions, and encouraged the participants to ask questions to ensure the participants understood the procedure during the test phase. At test, participants were shown forty-eight images in randomised order one at a time on screen; twenty-four original items (four from each of the six semantic categories) and twenty-four new items. Twelve of the original items were selected from the deep encoding stimuli and the remaining twelve from the shallow encoding stimuli. The correct YES / NO responses during encoding were divided equally across the twenty-four stimuli. The participants had to identify if they had seen each image during the study phase by pressing designated YES / NO keys on the keyboard. Each image remained on screen for a maximum of five seconds. Participants were encouraged to respond as quickly as possible. If they did not respond within the 5-second time limit the next image was automatically displayed. Each image was interspersed with an inter-stimulus interval screen

displaying a fixation cross for 250ms. All participants performed a 6-item practice session on the computer to ensure they understood the task instructions.

3.3 Results

Summary data are presented in Table 7.

3.3.1 Correctly identify previous studied pictures (hits)

To compare differences in remembering previously seen pictures (hit rates) between the deep and shallow processing conditions, a 2 x 3 mixed analysis of variance (ANOVA) was used, with LoP (deep, shallow) as the within participants factor and Group (WS, CA, MA) as the between participants factor. The ANOVA revealed significant main effects of Group [$F(2,57) = 3.83$, $p=.027$], and LoP [$F(1,57) = 87.624$, $p<.001$], but no Group x LoP interaction [$F(2,57) = 2.476$, $p=.093$]. See Figure 4.

Group: Tukey post-hoc comparisons revealed the main effect of Group was due to better performance by the CA group which was marginally above significance compared to both the WS and MA groups (both $p=.051$). There was no difference in hit rates between the WS and MA groups ($p=1.00$).

LoP: The significant main effect of LoP demonstrated a successful task manipulation, with a lower hit rate for shallow processed pictures ($p<.001$).

*Group*LoP:* Whilst the interaction between Group and LoP did not reach significance (*p*=.093) and suggests equivalent levels of semantic memory utilisation, effects sizes were calculated to aid in the interpretation of the data. These data revealed a notably smaller effect size between the LoP conditions for the WS group (*d*=0.90; p<.01) compared with both the CA (*d*=1.71; p<.001) and MA groups (*d*=1.66; p<.001). Controlling for correctly rejecting new items (described below) did not affect the pattern of LoP between groups.

Table 7: Hit rates and RT (ms) in deep and shallow encoding conditions, and new items for the WS, CA, & MA groups. SDs in parentheses

	WS	**CA**	**MA**
n	20	20	20
Deep hits %	80.1 *(19.1)*	95.5 *(7.4)*	88.1 *(11.0)*
Shallow hits %	60.8 *(24.5)*	67.7 *(21.5)*	52.8 *(21.5)*
New hits %	74.8 *(26.2)*	97.6 *(3.9)*	93.6 *(17.4)*
Deep RT ms	1544.26 *(649.19)*	979.75 *(320.27)*	1210.20 *(502.26)*
Shallow RT ms	1619.78 *(664.44)*	1180.25 *(352.40)*	1350.63 *(444.56)*
New RT ms	1641.09 *(584.45)*	990.11 *(248.97)*	1159.30 *(379.03)*

3.3.2 Reaction time (RT)

A 2 x 3 ANOVA with the same factors was applied to the RT data. Analyses revealed significant main effects of Group [F(2,57) = 5.305, *p*=.008], and LoP [F(1,57) = 18.237, p<.001], but no Group x LoP interaction [F(2,57) = 1.232, p=.299].

Group: Tukey post-hoc comparisons revealed the WS group's RT was significantly slower than the CA group's (p=.006), but there was no difference in RT between the WS / MA (p=.136) and CA / MA (p=.406) groups.

LoP: The main effect of LoP was due to significantly faster RT in response to previously studied '*deep*' items than '*shallow*' items (p<.001).

3.3.3 Correctly rejecting unstudied pictures (correct rejections)

A one-way ANOVA was conducted to identify group differences in correctly rejecting the new items. There was a significant effect of Group [F(2,59) = 8.931, p<.001]. The WS group made significantly more errors when identifying unseen items as new, compared to both the CA group (p=.001) and the MA group (p=.005), but no difference between the CA and MA groups (p=.752). There was also a significant difference between groups for RT to new items [F(2,59) = 12.509, p<.001]. The WS group were significantly slower than both the CA (p<.001) and the MA (p=.002) groups. The difference in RT between the CA and MA groups did not reach significance (p=.428).

3.4 Discussion

The aim of the current study was to investigate whether adults with WS (aged 35+yrs) could benefit from semantic support during encoding in an episodic memory task, thereby demonstrating greater recognition ability for information encoded at a deeper level compared with shallow encoding (Craik & Lockhart, 1972).

The results of the study upheld the first hypothesis; all groups significantly benefited from a semantic encoding strategy found in typically developing younger and older adults during LoP tasks (Luo et al., 2007; Troyer et al., 2006), evidenced by greater recall of items presented in the deep condition compared to the shallow condition. Under normal conditions, WS individuals find the encoding of new information into memory problematic and may adopt inefficient strategies while forming a new memory trace. In the present study, by encouraging participants to create a rich representation in memory by assessing whether the study item is part of a category, this aided performance compared to a shallow encoding strategy. This suggests that the documented atypical relationship between LTM and semantic memory in WS (Purser et al., 2011; Vicari et al., 2005) can be offset to some extent when the research paradigm incorporates lower levels of task demands (e.g. semantic fluency, Thomas et al., 2006) and provides greater levels of environmental support at retrieval (e.g. priming, Tyler et al., 1997). This also emphasises how incorporating pictorial stimuli in research with this group can help offset the more demanding contextual integration deficits observed when using verbal task paradigms (Hsu, 2013). The pattern of data presented here is in contrast to the lack of LoP effect observed in individuals with ASD (Mottron et al., 2001 Toichi & Kamio, 2002). Similarly, it also does not support previous research with individuals with WS, who demonstrated no bias for items encoded with either shallow or deep processing in a free-recall STM paradigm (Laing et al., 2005). However, the current study employed cued-recall of items from LTM, thus the differences between the current study and Laing et al. (2005) are likely due to the differences between these memory

paradigms as well as the modalities (verbal vs. visual). However, inspection of RT during recognition of previously studied items provides a measure of efficiency of episodic remembering. Here the WS group's RT was slower during recall compared to the CA group, which tentatively suggests that individuals with WS may have less efficient search processes when accessing LTM compared to age-matched controls, even though the paradigm was notably less demanding here than in Chapter 2.

When considering the overall recognition ability, the results partly upheld the second hypothesis. Even though an arguably less demanding episodic recognition memory task was employed, the episodic memory performance of the WS group was relatively impaired compared to the CA group but not the MA group; thus results indicate that the WS group were able to encode and subsequently remember episodic information at a level comparable to their verbal mental age. This would suggest that their deficits in episodic memory are interlinked with their general level of intellectual functioning. Therefore, episodic remembering using an 'easy' picture recognition paradigm, accompanied with a deep level of encoding and high environmental support at retrieval as employed here, still shows performance in adults with WS at a verbal mental age level. In the typically ageing literature, the extent of episodic memory deficits ranges from tasks that have no environmental support (free recall, with no cues present), moderate support (cued recall, e.g. semantic categories), to a great deal of environmental support which is present when the study material is represented in the test phase (recognition; Naveh-Benjamin, 2000). Interestingly, research investigating age effects on associative and episodic memory have found that

when semantic memory is heavily involved during the retrieval of previously studied items age differences tend to disappear (Nyberg et al., 2003). For instance, when recalling semantically related pairs in a paired-associate episodic memory task or retrieving overlearned (but demanding) information age differences are removed or minimised (see, for example, Riby et al., 2004a).

One caveat is that, after inspection of the effect sizes between the deep and shallow hit rates, there was a very large effect in both the CA and the MA groups. In contrast, the WS group's effect size, whilst still large, was notably smaller than the two comparison groups, due to the numerically lower hit rate and greater variability of performance in the deep condition. Such measures have been useful in examining controlled processing and monitoring mechanisms involved in episodic memory (e.g. Gallo, 2004; Johnson, 2006) and may contribute to the research highlighting executive frontal lobe dysfunction in WS (Mobbs, Eckert, Mills et al., 2007; Rhodes et al., 2010). During retrieval, monitoring processes are engaged when there is uncertainty when making a judgement regarding the status of a test item (Yonelinas, 2002). This is interpreted as evidence for overall impairments in episodic memory in WS during a LoP task, as previously noted in the WS literature (Nichols et al., 2004; Sampaio, Sousa, Férenandez, Henriques, & Gonçalves, 2008).

The EF deficits associated with the syndrome (Rhodes et al., 2010) are further emphasised by the WS group's significantly larger FA rate when rejecting new items, compared with the CA and MA groups whose hit rates approached ceiling level. An increase in FA errors rather than a decrease in hits are indicative

of executive dysfunction in individuals with WS (Menghini et al., 2010), and is the result of behavioural impulsivity due to atypical inhibitory functioning (Foti et al., 2015). Greater FA rates were evident in adults with WS in Chapter 2. In the current study, the WS group made significantly more FA errors when rejecting new items, compared with the CA and MA groups. This pattern was accompanied by slower RT when correctly rejecting new items. Greater susceptibility to false memories suggests that the recognition paradigm employed here did not produce a situation where the new items were distinctive enough to be rejected as an unstudied item. Thus, an increase in FA errors and greater RT during correct rejection in WS suggests uncertainty identifying an unstudied item. Despite more consideration and monitoring of responses, more false memories occurred for the WS participants. Elsewhere, in the spatial domain poor error monitoring has been seen to be a key characteristic of the WS profile (Rhodes et al., 2010; Smith, Gilchrist et al., 2009).

To conclude, this study has demonstrated that, under conditions of cued recall, adults with WS (aged 35+yrs) presented a LoP bias with greater recall of deeply encoded items than shallow encoded items. However, a smaller effect size in the WS group accompanied with greater FA rates and increased RT in response to new items was indicative of executive dysfunction due to deficits in error monitoring processes. The results emphasise the role of atypical EF processes in WS. Moving on, this is investigated in the next Chapter which will examine atypical attentional and inhibitory processes in WS using the Sustained Attention to Response Task (SART).

Chapter 4: Study 3 – Sustained Attention to Response Task

4.1 Introduction

The results from Chapters 2 and 3 have highlighted the importance of exploring the area of EF within the cognitive profile (e.g. Rhodes et al., 2010), since the successful engagement of such processing mechanisms is closely related to everyday cognitive ability. The results presented thus far in the thesis indicate that focus should be primarily on response inhibition and lapses of attention, as these are executive skills with clear implications for understanding wider deficits related to facets of the WS phenotype (e.g. the inability to inhibit inappropriate social approach behaviour, Little et al., 2013).

EF is an umbrella term that encompasses a range of higher order cognitive processes that control and regulate functions such as working memory, problem solving, planning, divided attention and inhibition, and which are predominantly controlled by frontal brain regions (Alvarez & Emory, 2006). In research exploring EF in WS, there is no consensus regarding the precise components of executive ability that are more or less impaired. However, in a recent paper, Costanzo, Varuzza et al. (2013) examined a variety of executive function tasks in children, and younger and older adults with WS (aged 11–35yrs) compared to individuals with DS and MA matched typical controls. Planning ability was particularly compromised in the WS group, with mixed results found in categorisation and inhibition, particularly with regards the modality of the tests employed (i.e. visual

vs. auditory tasks yielded inconsistent results; also see Osório et al., 2012 who employed a battery of EF tasks including WM, inhibition, and shifting, and found each related differently to IQ in both individuals with WS as well as those developing typically, though the magnitude between these EF processes and IQ was greater in the WS group).

As outlined in the thesis thus far, research has suggested that some individuals with WS share EF characteristics with individuals who have ADHD (Rhodes, Riby, Fraser, & Campbell, 2011). Whilst a comorbid ADHD diagnosis is relatively more common in WS (64%; Leyfer et al., 2006) than in other disorders such as DS (6–8%; Dykens, 2007), recent evidence from parental reports suggests that ADHD may be underdiagnosed in WS (Rhodes, Gillooly, & Riby, 2014). Importantly, ADHD is a neurodevelopmental disorder characterised by impaired attention, hyperactivity, impulsivity (American Psychiatric Association, 2013, Sonuga-Barke & Taylor, 2015) and disinhibition (Rhodes et al., 2011) and which is linked to executive-frontal lobe deficits (Willcutt et al., 2005; but also see Castellanos & Proal, 2012). Focusing specifically on inhibition, possible primary, and at least secondary, causes of the behavioural deficits observed in ADHD can be explained by disinhibitory deficits (see Johnstone, Barry, & Clarke, 2013, for a review of the ERP literature on ADHD). Recent fMRI work in WS has demonstrated that the executive impairment observed in this group mirrors the patterns seen in ADHD (Mobbs, Eckert, Mills et al., 2007). Their study employed fMRI methodology while participants with WS (aged 15–48yrs) performed a *Go / No-Go* measure of sustained attention and inhibition. The authors concluded that observed dis-engagement of the frontal-striatal networks of the brain contributed

to the complex pattern of social and behavioural deficits associated with WS (also see Hocking et al., 2013 who examined dual tasking and inhibition in the motor domain). In summary, work that has administered batteries of EF tasks has been inconclusive, while those studies that have specifically examined inhibition are promising in pinpointing the precise executive cognitive processes impaired in WS.

It has been noted that EF has been linked to other facets of the WS phenotype. Cognitive aspects of inhibition can be linked to a social phenotype characterised by a tendency to indiscriminately approach both familiar and unfamiliar people (Järvinen-Pasley et al., 2010; Jones et al., 2000). Using Cluster Analysis to explore heterogeneity of social approach within WS, Little et al. (2013) observed that the participants who showed most indiscriminate and atypically heightened approach ratings to unfamiliar faces were also those individuals who struggled with the Sun–Moon inhibition task (as opposed to relating to emotion processing ability or intellectual capability). The authors proposed that the finding provided preliminary support for a frontal lobe hypothesis of atypical social behaviour within the disorder. The study emphasised the necessity to explore inhibition abilities in individuals with WS due to their link to other facets of the disorder (see Barak & Feng, 2016, for a review of neurobiological and neuropsychological theories of atypical social behaviour in WS).

The first aim of the current study was to investigate inhibitory processing in adults with WS (aged 35+yrs). It is not unreasonable to predict particular inhibition deficits in an older WS sample given 1) typically developing older adults

suffer from executive deficits (see frontal ageing hypothesis; Greenwood, 2000; inhibition deficit hypothesis; Hasher & Zacks, 1988), and 2) considering the suggested premature cognitive ageing outlined in the General Introduction and Chapter 2 (Devenny et al., 2004; Krinsky-McHale et al., 2005). For these reasons, the study also incorporated an elderly TD comparison group to help in the data interpretation. The second aim was to employ a task that would enable a comprehensive examination of lapses of attention and inhibition which had previously been demonstrated to be related to real world activities in other populations, including ageing (Carriere, Cheyne, Solman, & Smilek, 2010), individuals with a neurodevelopmental disorder (e.g. ADHD; Johnson et al., 2007), as well as TBI (see Smilek et al., 2010, for discussion). The paradigm used was the Sustained Attention to Response Task (SART; Robertson et al., 1997; Smallwood, Riby, Heim, & Davies, 2006), a vigilance task which required the participant to respond to a frequent non-target stimulus and withhold a response to an infrequent target stimulus. From this, three main measures were obtained. First, false alarm (FA) commission errors, where participants fail to inhibit a response to non-target infrequent stimuli, were inspected as a measure of automaticity and inhibition. Secondly, and notably the most sensitive measure, pre- and post-error RT after a commission error were analysed to identify error monitoring abilities. Smallwood and colleagues (2006) use this approach and argue that after a FA error, attention tends to be re-directed back to the task after a period of task disengagement, resulting in slower RTs. Finally, as a general measure of task engagement, differences in the variability of RT during the task were gathered as a further measure of attentional lapse (see Dockree et al., 2004; Smallwood et al., 2006).

The study aimed to elucidate how inhibitory deficits observed in older adults with WS (aged 35+yrs) during the SART compared with TD adults matched for chronological age (CA), and with a group of TD older adults aged 65 years and over (65s). It was hypothesised that: 1) the WS group would have greater deficits in failing to withhold a response compared with the CA, with performance more comparable to the over 65s groups with known difficulties in inhibitory control (Greenwood, 2000); 2) there would be no difference in the WS group's RT before and after a failure to withhold a response, similar to other populations with known deficits in error monitoring and executive control (e.g. TBI, Robertson et al., 1997), whereas both the CA and the 65s groups would show an increase in RT post-error reflecting an ability to learn from the commission errors (of note, despite the widely documented executive controlled deficits with increasing age, error monitoring in the context of a sustained attention tasks appears spared, e.g. McVay, Meier, Touron, & Kane, 2013); and 3) there would be more variability in RT overall during the task reflecting a deficit in task engagement and attentional lapse in the WS group compared to the CA and the 65s groups.

4.2 Method

4.2.1 Participants

Three groups made up the sample for this study; adults with WS aged 35+yrs (WS), TD adults matched for chronological age (CA), and a group of TD older adults aged 65+yrs (65s). Data collection for this study took place during

the same testing session as in Chapter 2 (see *section 2.2.1* for participant demographic details).

4.2.2 Materials

The SART is a vigilance task during which participants had to respond to a frequent non-target (the letter 'X') and withhold a response to an infrequent target (the letter 'Y'). Stimuli were presented on screen in Courier New font, size 28. Stimulus duration was 300ms interspersed by an inter-stimulus fixation cross presented for 900ms. There were 6 blocks of 20 stimuli, with 120 stimuli in total. The 'Y' stimulus frequency was 20%, with targets and non-targets presented in fully randomised order. The task was programmed using Eprimev2.00 (Schneider et al., 2001) and stimuli were presented on a Toshiba laptop with a 12" screen. A4 laminated examples of the stimuli were used as visual aids for all participants during explanation of the task.

4.2.3 Procedure

Details regarding testing session's locations and informed consent were as per Chapter 2. Before beginning the SART the participants were presented with the following instructions:

> *"In this task you will see the letters X and Y appear on the screen. Your task will be to push the spacebar whenever you see the letter X. Do nothing when the letter Y appears on the screen. We would like you to give equal weight to responding to the stimulus and also to minimising errors."*

These instructions were reiterated verbally by the experimenter and the participants shown the laminated examples of the stimuli. All participants

performed a practice block of 10 stimuli (9'X's / 1'Y') prior to performing the main session. Task duration was approximately 4min.

4.3 Results

Summary data are presented in Table 8.

4.3.1 False alarm commission errors (frequency of failures to withhold on the SART)

The mean probability of making a commission false alarm (FA) error was considered in a univariate analysis of variance (ANOVA), with Group as the between subjects factor. There was a main effect of group on FA rates [$F(2,59) = 7.832$, $p=.001$]. Tukey post-hoc analyses revealed the WS group made significantly more FAs than the 65s group ($p=.001$) but not the CA group ($p=.207$). The difference between the CA and the 65s groups approached significance ($p=.075$) in that the over 65s made fewer FAs.

4.3.2 Reaction time (RT)

The analysis was repeated on the RT when making a FA. The ANOVA identified a main effect of group on RT [$F(2,59) = 10.035$, $p<.001$]. Tukey post-hoc analyses found the WS group's RT when making a FA was significantly slower than the CA group's ($p=.009$) but not the 65s group's ($p=.418$). There was a significant difference between the CA and the 65s groups ($p<.001$) where the CA group's RT was significantly faster.

4.3.3 Hit rates for the frequent non-target stimuli (hits)

ANOVA were also applied to hit rates (correctly responding to the non-target). A significant main effect of group was observed [F(2,59) = 30.677, p<.001]. The WS group's hit rate was significantly lower when responding to the non-target than both the CA and the 65s groups (both p<.001), while the CA group's hit rate was significantly greater than the 65s group (p=.05).

4.3.4 Reaction time (RT) to hits

The ANOVA also revealed a significant main effect of RT to hit rates [F(2,59) = 15.913, p<.001]. Tukey post-hoc analyses revealed no difference in RT between the WS and CA groups (p=.943), but significantly longer latency by the 65s group when responding to the non-target than both the WS and CA groups (p<.001).

Table 8: Percentage FAs (failure to withhold a response) and mean RT (ms), percentage hit rates and mean RT (ms) on the full SART. Mean RT (ms) of two correct hits before and after a failure to withhold a response

	WS	**CA**	**65s**
Full SART			
N	20	20	20
False alarms %	9.5 *(4.4)*	7.6 *(3.0)*	5.2 *(2.6)*
False alarms RT ms	322.83 *(45.58)*	289.96 *(21.32)*	336.34 *(29.50)*
Hits %	47.6 *(27.9)*	92.6 *(0.8)*	78.5 *(0.1)*
Hits RT ms	334.88 *(51.95)*	338.57 *(27.49)*	391.71 *(18.94)*
SART before / After			
n	8	17	10
RT ms *(SD)* before	324.41 *(77.25)*	307.15 *(48.60)*	352.97 *(55.66)*
RT ms *(SD)* after	314.34 *(106.29)*	346.76 *(44.20)*	384.52 *(60.26)*

4.3.5 Reaction time (RT) before and after a failure to withhold a response

In order to identify the effect of a failure to withhold a response on RT and error monitoring by the participants, the mean RT was calculated on the two stimuli presented immediately before and immediately after each FA. Data were only included in the mean if a participant correctly responded to four non-target stimuli (i.e. two responses before and two responses after an error), resulting in RT data from eight of the WS group, seventeen from the CA group and ten from the 65s group being included in this analysis.

Separate t-tests for each group (WS, CA, and 65s) were employed to compare their RT before and after a FA commission error. The WS group's RT before and after a FA did not differ [t(7) = 0.196, p=.85, *d*=0.15]. In contrast the CA group's RT was significantly slower RT post-FA [t(16) = 3.329, p=.004, *d*=1.67], whilst the latency in the 65yr group approached significance [t(9) = 2.251, p=.051, *d*=1.5]. See Figure 4.

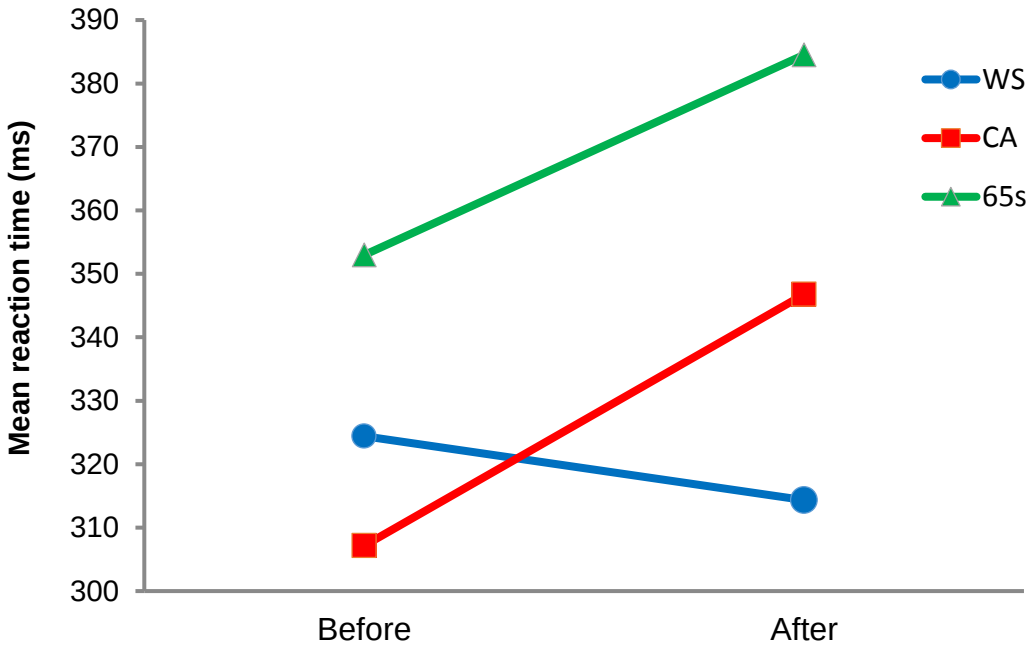


Figure 4: Mean reaction time (RT) in ms of responses before and after a failure to withhold a response

4.3.6 Mean variability in RT during performance of the SART

ANOVA were also applied to the measure of task variability (SDs of response time throughout the whole task for each participant). A significant main effect of group was observed [$F(2,57) = 26.48$, $p<.001$]. Tukey post-hoc analyses revealed greater variability in the WS group compared to both the CA and the over 65s (both $p<.001$). There was no difference in variability between the CA and the 65s groups ($p=.67$). See Figure 5.

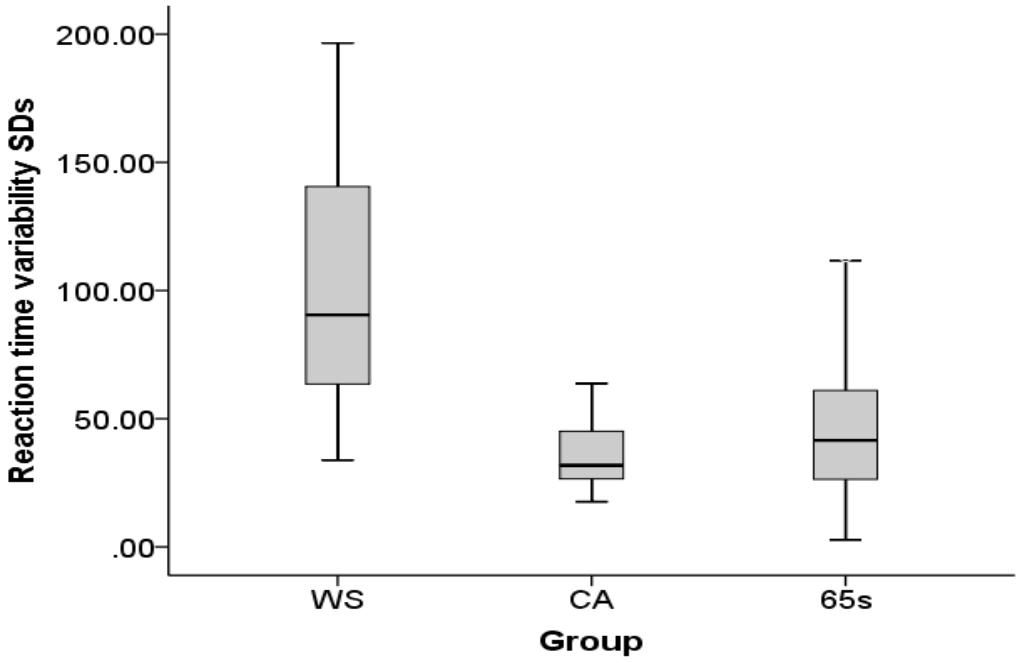


Figure 5: Mean variability in RT (ms) during the task across the WS, CA, & 65s groups. Error bars represent SDs

4.4 Discussion

The aim of this study was to investigate atypical attentional and inhibitory processes which may subserve the episodic and semantic memory deficits described in Chapters 2 and 3. The most notable findings from the current study were the FA errors of commission to the infrequent target stimuli, and the RT pre- and post-error. Robertson et al. (1997) argue that, as well as errors being an indicator of poor inhibition, quicker responses prior to and decrease in RT following an error are due to a shift of controlled cognitive processing into a more automatic response style, thus reflecting impaired sustained attention to the task. In contrast, post-error slowing after a FA commission error is an important indicator of the EF of error monitoring and the re-establishment of controlled processing during sustained attention. In the present study, both the CA and the

65s groups' RT increased post-error, and is supported by the large effect sizes. Of note, whilst the difference in the 65s RT pre- and post-error was not significant, this likely reflects the reduced sample size (n=10). Notably, this increased RT in the 65s group, whilst non-significant, supports previous research demonstrating that this aspect of EF is relatively well preserved in TD older adults (McVay et al., 2013). In contrast, the WS participants did not follow this pattern, with no difference in RT pre- and post-error, and emphasied by the small effect size. Rather, their performance was in line with other populations with known frontal lobe and associated executively controlled processing deficits (e.g. TBI; Robertson et al., 1997; see also Dockree et al., 2004). This suggests that, under conditions of automaticity brought on by the presentation of long streams of non-target stimuli, these individuals with WS were unable to re-establish executive control of behaviour to maintain sustained attention performance. Deficits in error monitoring linked to impaired spatial cognition in WS have been highlighted previously in the thesis (in the visual domain; Smith, Gilchrist, et al., 2009). However, it is important to exercise caution in the interpretation of the data from the current study, as an insufficient number of trials available to create a mean in some participants resulted in the reduced sample size in this analysis.

When considering the FA rate in the younger and older control participants, the results found FA commission errors were greater in the CA group, but this difference was accompanied by slower responses for the 65s group. Although this finding failed to reach significance, it seems plausible that the elderly participants' performance reflected a speed–accuracy trade-off widely documented in the literature, whereby older adults attempt to compensate and

minimise errors during task completion (Starns & Ratcliff, 2010; also see Chapter 2). In contrast, the WS participants produced the highest FA commission errors (significant for the 65s vs. WS comparison). This alone suggests an inhibition deficit, especially when considering their RT was equivalent to the 65s group and slower than the CA controls. Furthermore, the increased RT for the WS group did not lead to reduced FAs as a speed–accuracy trade-off as observed in Chapter 2; rather it mirrors the profile observed in ADHD (see Geburek, Rist, Gediga, Stroux, & Pedersen, 2013, for a meta-analysis). This finding is consistent with inhibition deficits found on more traditional neuropsychological measures (e.g. West, Schwarb, & Johnson, 2010), and work suggesting that ADHD characteristics are also associated with WS (Rhodes et al., 2011).

As a general measure of attentional lapse and task engagement, the mean hit rates to the frequent non-target stimuli were considered. The hit rate in the WS group was low (WS, 48% cf. CA, 93% & 65s, 79%) and the standard deviation was high (28%), which was not surprising considering the cognitive heterogeneity known to be associated with the syndrome (Porter & Coltheart, 2005). The analysis of variability on the RT throughout the duration of the task also demonstrated that the WS participants were unable to exert controlled processes to maintain focus during the task (also see Tye et al., 2016, who discuss reaction time variability as a marker of ADHD). Both the CA and the over 65s were comparable, but for the WS group a lapse of attention in general was evident as well as an inability in learning from a commission error. Sustained attention metrics including RT variability have been used in previous research when assessing the key cognitive markers of ADHD and have proved to be strong

predictors of impairment (Williams et al., 2010), further highlighting the similarities in the cognitive difficulties observed between WS and ADHD (Rhodes et al., 2010, 2011; but also see Coghill et al. (2014) who found only 18% of their sample were impaired on response variability).

Considering how atypicalities in executive processes of attention and inhibition can be attributed to the social, behavioural, and cognitive phenotypes in WS, future research would benefit from further investigation of the underlying neurocognitive mechanisms sub-serving these inhibition impairments. Previous fMRI research has linked these impairments to deficits in fronto-striatal network (Mobbs, Eckert, Mills et al., 2007) and under-connectivity between the amygdala and pre-frontal cortex (Meyer-Lindenberg, Hariri et al., 2005; but also see Barak & Feng, 2016). Similarly, converging evidence from ERP studies, with the aim pinpointing the temporal dynamics of inhibition deficits (see N200 work; e.g. Schmajuk, Liotti, Busse, & Woldorff, 2006), would be beneficial. In other domains such as face processing, ERPs have been successful at pinpointing the processing mechanisms impaired and spared (e.g. Key & Dykens, 2011, 2015; Mills et al., 2000).

Finally, the aforementioned results show the benefit of including a sample of TD older individuals, in that the results seen in the WS group cannot be linked directly to an ageing hypothesis or interpretation. Exploring any possible association with ageing in the WS group was a central aim of the current study. However, it would have also been useful to include a group of TD children of

comparable mental age to ensure that the pattern of findings for the WS sample was not associated with mental capacity.

To conclude, the current study identified a series of controlled processes related to inhibition and attentional lapse to be problematic for older adults with WS, and which could not be related to possible premature cognitive ageing. Failing to withhold a response, re-engaging attentional control processes after an error, and an overall deficit of concentration and task engagement was evident. Thus, under certain conditions, a deficit in executive control prevents WS adults effectively monitoring and shifting from automatic to control modes of processing. The final two studies of the thesis will investigate the neural mechanisms that may sub-serve the observed behavioural attentional and inhibitory deficits.

Section B: Introduction to the electrophysiological phase of the thesis

In the behavioural section of the thesis, the main findings were: 1) an inability by adults with WS to capitalise on semantic memory during associative memory tasks with low environmental support (Chapter 2); 2) the ability to benefit from semantic memory when provided with high levels of environmental support (Chapter 3); and 3) an overall deficiency in attentional processing and inhibitory control in a *Go / No-Go* paradigm (Chapter 4). The Methodological considerations section of the General Introduction (*section 1.3*) highlighted the limitations when adopting behavioural-only paradigms when researching cognitive functioning in individuals with developmental disorders. Thus, the electrophsysiological section will focus on the neural mechanisms that may underpin the behavioural deficits described in Chapters 2, 3 and 4, by employing event-related potentials (ERP) and electroencephalography (EEG) methodologies. Two studies make up the electrophysiological phase of the PhD: 1) the three stimulus Oddball task (Chapter 5), which is highly sensitive to temporal precision of the ERPs elicited during involuntary and voluntary attentional and inhibitory processes, and 2) an Eyes Closed / Eyes Open paradigm (Chapter 6) which measures the spectral power of the cortic-electrical frequency bands during resting states.

Chapter 5: Study 4 – Oddball Task, ERP Methodology

5.1 Introduction

In Chapter 4 of the thesis it was noted that, in the SART, adults with WS demonstrated overall impairment in attentional processing, and more specifically, a profile of inhibitory deficits similar to those found in typically developing individuals who have suffered a TBI (Robertson et al., 1997), albeit not as severe.

Particularly relevant to the current investigation, Mobbs, Eckert, Mills et al. (2007) highlighted the role of atypical fronto-cortical activity during inhibitory processing in WS. Employing fMRI methodology and a *Go / No-Go* paradigm, Mobbs and colleagues (2007) compared the functional profile of eleven individuals with WS (mean age 31yrs 5mths, SD 12yrs 2mths) and eleven typically developing individuals matched for chronological age and gender (mean age 30yrs 3mths, SD 11yrs 2mths). Despite comparable group behavioural performance (accuracy but not RT), compared to the typical controls, the WS group's BOLD activity was significantly reduced in the striatum, dorsolateral prefrontal, and dorsal anterior cingulate cortices, and increased activity in the posterior cingulate cortex on presentation of *No-Go* trials. This demonstrates that, irrespective of behavioural similarities, these individuals with WS a) failed to activate the fronto-cortical and subcortical structures associated with behavioural inhibition, and b) presented hyperactivity in posterior regions which, in ADHD,

has been linked with a reduced ability to relocate attention after an error (Sergeant, 2000), and which was a main finding of the SART study (Chapter 4).

The neuroimaging methodologies outlined in the General Introduction (*section 1.2.1*) have enabled researchers to identify the spatial and functional mapping of fronto-cortical networks recruited during inhibitory processes in both typically and atypically developing individuals. The temporal precision obtained from ERP methodology pinpoints with millisecond accuracy the neural responses associated with behavioural performance. One paradigm highly sensitive to the ERPs associated with involuntary and voluntary attentional processes is the three-stimulus Oddball task (Donchin et al., 1978), whereby participants respond to an infrequent target stimulus while withholding their response to two distractors; a frequent non-target stimulus and an infrequent novel stimulus. The three main ERP components elicited are sensitive to novelty detection (novel N2 / P3a, both observed fronto-centrally) and cognitive control (target N2 / P3b, both observed centro-parietally) (Folstein & Van Petten, 2008; Polich, 2007). (The Oddball task and ERP components were described in detail in *section 1.2.3* of the General Introduction.)

Whilst the Oddball paradigm has been used widely in a variety of research including TD individuals (Barron et al., 2011), clinical and subclinical populations (e.g. schizophrenia: del Re, 2014; eating disorders: Osborne & Riby, 2016), and developmental disorders (e.g. ADHD: Barry, Clarke, McCarthy et al., 2009); ASD: Cléry et al., 2013); to date the Oddball task as described in the thesis has not been employed in research with individuals with WS. However, one recent study

(Key & Dykens, 2011) adopted an Oddball style paradigm to investigate global / local stimulus discrimination in a group of adults with WS during a Navon style visuo-spatial task (n=12, mean age 26yrs 3mths, SD 8yrs 4mths), compared with a control group matched for chronological age (n=16, mean age 29yrs 7mths, SD 11yrs 9mths). Participants had to identify a target letter which was presented in either global or local hierarchy, and displayed with equal probability (20%). The task instructions were generalised to avoid biasing participants' attention to either the global or local level, thus both levels were novel and target stimuli. Both groups' ERP profile included a frontal P3a response indicative of involuntary orienting to a rare stimulus, but the WS group presented prolonged P3a latencies in response to both levels, and attenuated P3a amplitude in response to the local stimulus suggesting insufficient allocation of attentional resources to local features. No centro-parietal P3b discrimination between global and local targets was observed in the WS group, whereas longer P3b latencies were found in both control groups in response to the local targets suggesting greater recruitment of attentional resources. No details relating to the N2 component were provided. These results are indicative of impaired effortful processing when greater attentional resources are required, as would be the case during local stimulus discrimination.

Other ERP studies also indicate atypical activity in WS in components / cortical regions elicited by the Oddball task, with an atypically enhanced N2 response to matched and mismatched face stimuli (Mills et al., 2000), and an attenuated amplitude but prolonged frontal response to inverted faces (Grice et al., 2001). Combined, these studies suggest WS is characterised by an atypical

neural signature in both the early sensory / perceptual and later controlled processes.

As outlined in the General Introduction (*sections 1.1.3* and *1.1.9*), WS is characterised by many characteristics associated with ADHD, and also ASD to a lesser extent (Tordjman et al., 2012). With regard to neural signature that may be predicted in WS during a visual three-stimulus Oddball task, inspection of the ADHD and ASD literature has proved promising in elucidating the neural mechanisms recruited. Barry, Clarke, McCarthy et al. (2009) adopted a bi-modal (auditory target and visual non-target) three-stimulus Oddball design with ADHD adults (n=18, age 18–26yrs, mean 21yrs 11mths, SD 1yrs 9mths) and a CA-matched typically developing control group (demographic details not supplied). An attenuated fronto-central N2 peak amplitude was observed in the ADHD group in response to the visual non-target stimulus compared with the controls, with the difference at the central site approaching significance (p=.06). There were no group differences in target N2 peak amplitude, and non-target and target N2 peak latencies. There were also no differences in both the P3a and P3b peak amplitudes and peak latencies between ADHD and controls, which the authors suggest may be due to more effortful processing by the ADHD group. Similarly, Sokhadze et al. (2009) adopted a visual three-stimulus Oddball paradigm with children and young adults with ASD (n=11, aged 9–27yrs, mean age 16yrs 9mths, SD 5yrs 4mths), and a TD control group (n=11, age 11–27yrs, mean age 19yrs 5mths, SD 6yrs 4mths). They found no group difference in N2 / P3a peak amplitude, whereas the ASD group presented longer N2 / P3a peak latencies in response to the novel stimulus indicative of a delay in orienting to novelty

response. There were no group differences in P3b peak amplitude, but prolonged P3b peak latency by the ASD group which the authors interpreted as impairments in sustained attention. However, a series of studies adopted both auditory and visual *Go / No-Go* paradigms in ADHD found mixed findings (e.g. Fallgatter et al., 2005; Prox et al., 2007; Townsend et al., 2001; Wiersema, Van Der Meere, Roeyers, Van, & Baeyens, 2006); thus, comparison of Oddball ERP profiles across modalities should be interpreted with caution due to the recruitment of differing attentional neural mechanisms during stimulus detection (Crottaz-Herbette & Menon, 2006).

The aim of Chapter 5 was to characterise the neural signature of adults with WS during a visual three-stimulus Oddball task, and thus elucidate the neural mechanisms that may underpin the deficient executive control and inhibitory processing associated with the syndrome. Consideration needs to be given to whether the ERP profile observed in WS reflects their mental (i.e. developmental) age, or their chronological age. As such, two comparison groups were included in the study; a cohort of TD adults matched for chronological age (CA), and a group of TD children matched for verbal mental ability (MA). TD younger children display an age-associated ERP profile which reflects their ongoing neuronal maturational processes (as discussed in the Methodological considerations section of Chapter 1; also see Segalowitz & Davies, 2004; Stige et al., 2007). Thus, an ERP profile in adults with WS that is indicative of verbal mental age was not predicted; however the MA group are included in the study for completeness. Based on the previous ERP research with WS, ADHD, and ASD, and the findings in Chapter 4, a profile comparable with ADHD was predicted. Specifically, it was

hypothesised that, compared to the CA group, the adults with WS will present: 1) atypical early sensory processing indexed by attenuated N2 peak amplitude in response to the novel and target stimuli; 2) increased P3a latency reflecting a delay in the orienting to novelty response; and 3) increased P3b latency indicative of working memory and storage updating functioning.

5.2 Method

5.2.1 Participants

Three groups participated in the study; adults with Williams syndrome (WS), and two comparison groups consisting of a group of TD adults matched for chronologically age and gender (CA), and TD children matched for verbal mental ability (MA). Eleven older adults with WS (aged 37yrs 2mths–49yrs 3mths, mean age 42yrs 7mths, SD 4yrs 0mths) were recruited via the Williams Syndrome Foundation, and who were known to the research team. Nine had their genetic diagnosis confirmed with *FISH* testing, whilst the remainder had been diagnosed based on their clinical phenotype prior to the availability of genetic diagnosis. Seven of the WS group lived at home with their parents or with carers in sheltered accommodation, and four lived independently. Six were in some form of paid employment / volunteer work while the rest attended daycare centres or received state-provided care assistance.

The CA group consisted of sixteen typically developing adults (aged 36yrs 10mths–49yrs 2mths, mean age 42yrs 10mths, SD 4yrs 2mths) matched for chronological age. The MA group comprised of thirteen typically developing

children (aged 8yrs 7mths–15yrs 7mths, mean age 12yrs 2mths, SD 2yrs 8mths) and who were matched to the WS group for receptive vocabulary using the raw scores from the BPVS II (Dunn et al., 1997: WS, 116.82*, SD 10.36*; MA 117.54*, SD 12.98).*

Handedness from all participants was assessed using the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). Four of the WS group were left-handed, while all participants in the CA and MA groups were right-handed. The participants in the two comparison groups received £6.00 for their participation. This study received ethical clearance from the Psychology department ethics committee at Northumbria University. Written informed consent was provided by the WS group where possible and by all parents / carers of both the WS and MA groups.

5.2.2 Materials and procedure

The three-stimulus Oddball task was programmed and presented using E-Prime presentation software on a Toshiba laptop with a 14" monitor. The task comprises of frequent, novel, and target stimuli. The target stimulus (red circle, area = 12.6cm^2) appeared on 13% of trials, the standard frequent stimulus (green square, area = 16cm^2) appeared on 74% of trials, and the novel stimulus (blue square, area = 256cm^2) appeared on 13% of trials. Participants completed a 10-trial practice block. The testing phase consisted of 2 blocks of 150 trials each. Stimuli remained on screen for 250ms, and were followed by an inter-stimulus interval between 830ms and 930ms. Participants were instructed to press the space bar on a standard keyboard in response to the target stimulus and ignore all other stimuli. (For further discussion of the Oddball task, see Polich, 2003.)

The testing sessions with the WS group took place in their homes, with a parent / carer present at the session or nearby. The comparison groups' testing sessions took place in the Psychology department at Northumbria University or in the participants' own homes. The experimenter outlined the experimental procedure and invited each participant to read and sign an informed consent form and complete the EHI.

5.2.3 EEG recording

The EEG was recorded from thirty-two channels using an electrode cap (Biosemi, Amsterdam, The Netherlands). Electrode placement was based on the extended international 10–20 system (Klem, Lüders, Jasper, & Elger, 1999). The montage included four midline sites (FZ, CZ, PZ, OZ), fourteen sites over the left hemisphere (Fp1, AF3, F3, F7, Fc1, Fc5, C3, T7, Cp1, Cp5, P3, P7, Po3, O1), and fourteen sites over the right hemisphere (Fp2, Af4, F4, F8, Fc2, Fc6, C4, T8, Cp2, Cp6, P4, P8, Po4, O2). Additional electrodes were placed on the left and right mastoid for referencing purposes. Electrodes were placed above and below the left eye to record the vertical electrooculogram to assess eye blink movement.

5.2.4 ERP processing

All signals were digitised at a rate of 2048 Hz, with a recording epoch of 1,000ms (–200 to +800ms). Automatic eye blink correction, artefact rejection (values outside the range of −100 μV to +100 μV), and ERP averaging were carried out offline using Neuroscan SCAN 4.5 software (Compumedics, El Paso, TX). After eye blink correction and removal of trials with artefacts, the remaining

trials were used in the analysis of each group's responses, with a minimum of sixteen trials per condition / participant required for inclusion in the final data analysis. The components of interest were N2, P3a, and P3b, detected in the time frames 200–325ms, 310–450ms, and 380–600ms respectively. These data were obtained from the midline sites (FZ, CZ, and PZ) and where peaks were maximal (based on visual inspection of the grand average ERPs and previous research employing the Oddball task).

5.2.5 Data analysis

Ten of the WS group, thirteen of the CA-matched adults, and twelve of the MA-matched children were included in the final analysis. Data from one WS participant, three CA participants, and one MA participant were excluded due to high levels of EEG artefacts which compromised further analysis. The peak amplitude and latencies for the ERP components of interest from the remaining participants were investigated, with all analyses conducted using SPSS version 21. The between subjects factors were group (WS, CA, MA), and the within subjects factors were electrode site (FZ, CZ, PZ).

5.3 Results

ERP data were analysed with a 3 x 3 analysis of variance (ANOVA), with group (WS, CA, MA) as the between measures factor, and site (FZ, CZ, PZ) as the within measures factor. Follow-up / planned comparisons of group and site differences were investigated using t-tests. Results upheld Mauchly's test of

sphericity unless stated. Where this test was violated, a Greenhouse-Geisser correction was applied to the results.

5.3.1 P3a and P3b results

The P3a and P3b amplitude data were calculated by subtracting the peak amplitude of the frequent stimulus from the peak amplitude of the novel (P3a) and target (P3b) stimuli, thus the P3a and P3b amplitude data is the mean difference in peak amplitude between these conditions (see Polich, 2007). The P3a and P3b latency data were calculated from the mean of the raw peak latency scores in response to the novel (P3a) and target (P3b) stimuli. Descriptive statistics for the mean peak amplitude and mean peak latency for the P3a and P3b components are presented in Table 9 and Table 10 respectively.

Table 9: Mean peak amplitude (μv) and peak latency (ms) for P3a (SDs in parentheses) for the WS, CA, & MA groups at FZ, CZ, & PZ electrode sites

	Amplitude			**Latency**		
	WS	CA	MA	WS	CA	MA
FZ	**11.83** *(5.31)*	**13.30** *(3.83)*	**11.31** *(13.10)*	**413.50** *(16.82)*	**388.78** *(20.39)*	**380.63** *(44.30)*
CZ	**13.99** *(4.75)*	**14.21** *(4.34)*	**17.52** *(17.37)*	**418.77** *(18.4)*	**396.78** *(19.1)*	**393.4** *(59.03)*
PZ	**9.27** *(5.29)*	**9.51** *(4.69)*	**14.85** *(13.13)*	**415.11** *(57.65)*	**408.46** *(43.08)*	**395.72** *(61.25)*

5.3.1.1 P3a amplitude

There was no significant main effect of group on P3a amplitude [$F(2,32) = .325$, $p=.725$]; whereas a significant main effect of site [$F(2,64) = 11.53$, $p<.001$], and a significant Site x Group interaction [$F(4,64) = 3.69$, $p=.009$] were observed.

Site: The main effect of site was due to significantly greater P3a amplitude at CZ compared to both FZ ($p=.005$) and PZ ($p<.001$).

*Site*group:* Paired samples t-tests revealed no difference in peak amplitude between FZ and CZ for both the WS and CA groups ($ps\geq.125$), whereas a significant increase in peak amplitude from FZ to CZ ($p=.014$) was observed in the MA group. In contrast, significantly greater peak amplitude at CZ compared with PZ was found in both the WS and CA groups (both $p<.001$), whereas no peak amplitude difference was observed between CZ and PZ in the MA group ($p=.197$). Significantly greater peak P3a amplitude was also observed at FZ compared with PZ in the CA group ($p=.006$), whereas no difference in peak amplitude between these sites was found in the WS and MA groups (all $p\geq.132$). The pattern of findings is summarised in Figure 6.

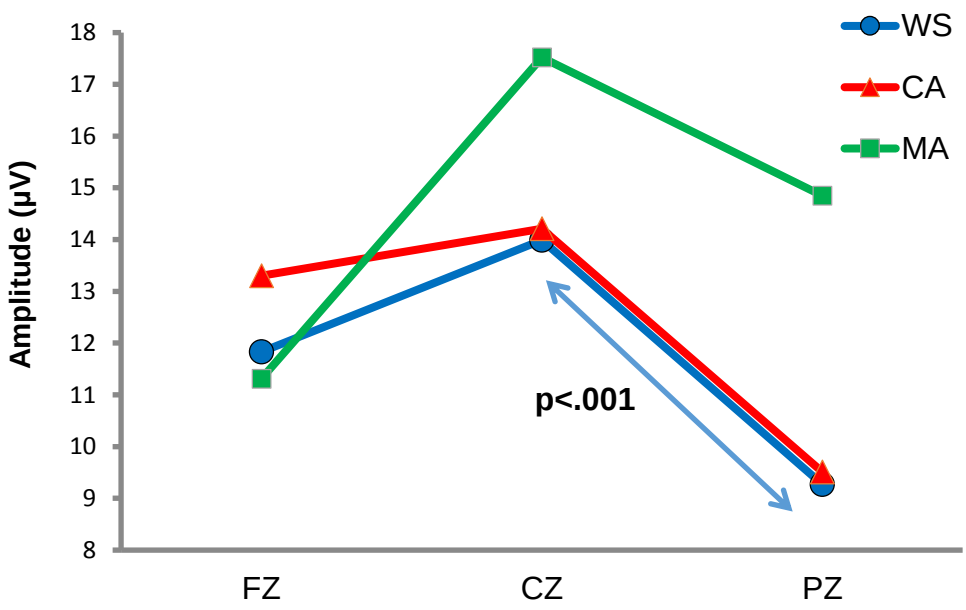


Figure 6: Mean peak P3a amplitude (µv) for the WS, CA, & MA groups at FZ, CZ, & PZ electrode sites

5.3.1.2 P3a latency

The analyses violated Mauchly's test of sphericity; therefore a Greenhouse-Geisser correction was applied to the P3a latency results. The ANOVA revealed no significant main effects of group [F(2,32) = 1.615, p=.215], or site [F(1.202,38.471) = 1.530, p=.227], and no Site x Group interaction [F(2.404,38.471) = .343, p=.750]. However, since the P3a is typically centred on fronto-central locations (confirmed above for WS and CA groups) it was appropriate to consider a more focused analysis. See Figure 7.

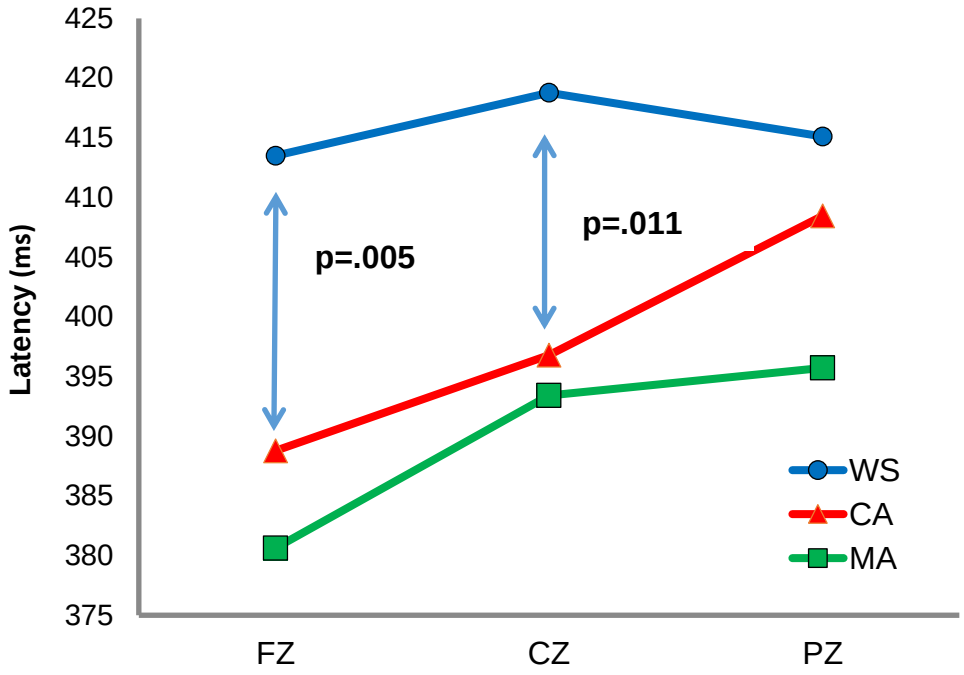


Figure 7: Mean peak P3a latency (ms) for the WS, CA, & MA groups at FZ, CZ, & PZ electrode sites

Independent samples t-tests identified significantly longer peak P3a latency in the WS group than the CA group at both FZ (p=.005) and at CZ (p=.011). The WS group's peak latency at FZ was also significantly delayed than was observed in the MA group (p=.032), but not at CZ (p=.181). There was no difference in peak P3a latency between the CA and MA groups at FZ and CZ (both p≥.555), and no differences between the WS, CA, and MA groups at PZ (all p≥.457). Paired-samples t-tests revealed a significant increase in peak P3a latency in the CA group by site from FZ to CZ, and from FZ to PZ (both p=.049), but not CZ/PZ (p=.214). There was no difference in peak latency by site observed in both the WS or MA groups (all p≥.093). In summary, the WS group presented a significant delay in fronto-central (FZ/CZ) latency compared with the CA group, and at frontally (FZ) compared to the MA group. See Figure 8 for the P3a component headmaps.

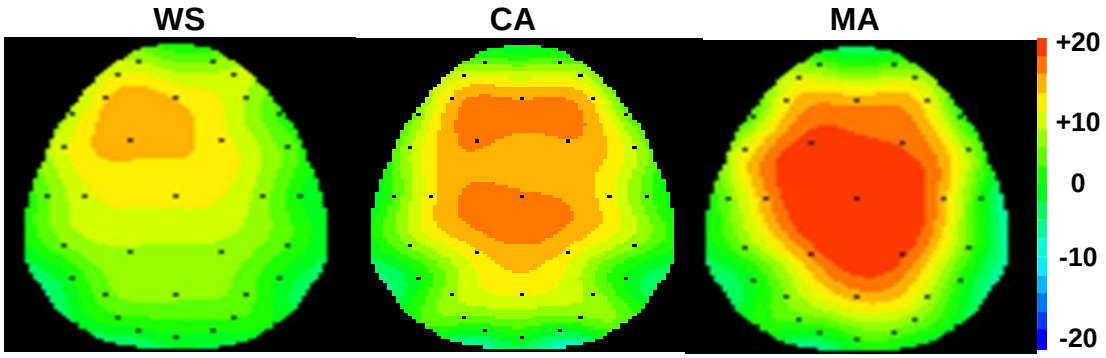


Figure 8: Headmaps for the P3a component in the WS, CA, & MA groups

P3a summary: Both the WS and CA groups presented a fronto-central distribution whereas a centro-parietal distribution was observed in the MA group. Despite the comparable amplitude between WS and CA, the increased frontal latency observed in the WS group suggests a temporal delay in their neural mechanism engaged in response to the novel stimulus.

5.3.1.3 P3b amplitude

Analyses violated Mauchly's test of sphericity: therefore a Greenhouse-Geisser correction was applied. The ANOVA identified a significant main effect of group [F(2,32) = 4.161, p=.025], no significant main effect of site [F(1.690,54.095) = .819, p=.428], and a significant Site x Group interaction [F(3.381,54.095) = 13.886, p<.001], on the P3b amplitude. See Figure 9.

Table 10: Mean peak amplitude (μv) and peak latency (ms) for P3b (SDs in parentheses) for the WS, CA, & MA groups at FZ, CZ, & PZ electrode sites

	Amplitude			**Latency**		
	WS	CA	MA	WS	CA	MA
FZ	**9.60** *(7.29)*	**9.79** *(6.14)*	**8.01** *(5.23)*	**459.39** *(78.90)*	**429.94** *(35.23)*	**341.85** *(119.49)*
CZ	**7.85** *(7.43)*	**4.43** *(7.25)*	**15.89** *(9.77)*	**486.79** *(47.01)*	**459.16** *(62.87)*	**437.47** *(124.82)*
PZ	**6.38** *(6.24)*	**6.22** *(6.63)*	**18.36** *(9.69)*	**429.76** *(82.31)*	**420.59** *(54.25)*	**456.10** *(79.87)*

Group: Tukey post-hoc comparisons revealed significantly greater P3b amplitude in the MA group compared to the CA group (p=.027). Comparisons between the WS group and both the CA and MA groups were non-significant (p≥.095).

*Site*group:* Follow-up comparisons using independent t-tests identified significantly greater peak P3b amplitude in the MA group compared with the WS group at both CZ (p=.045) and PZ (p=.003), and with the CA group at CZ (p=.003) and PZ (p=.001). In addition, paired samples t-tests found no difference in peak P3b amplitude between all sites in the WS group (all p≥.104), whereas the CA group's peak P3b amplitude was significantly greater at FZ compared with CZ (p=.001), FZ compared with PZ (p=.01), and increased in peak amplitude from CZ to PZ which approached significance (p=.068). The MA group's P3b amplitude significantly increased from both FZ to CZ (p=.004) and FZ to PZ (p=.002), but no there was no peak amplitude difference between CZ and PZ (p=.175).

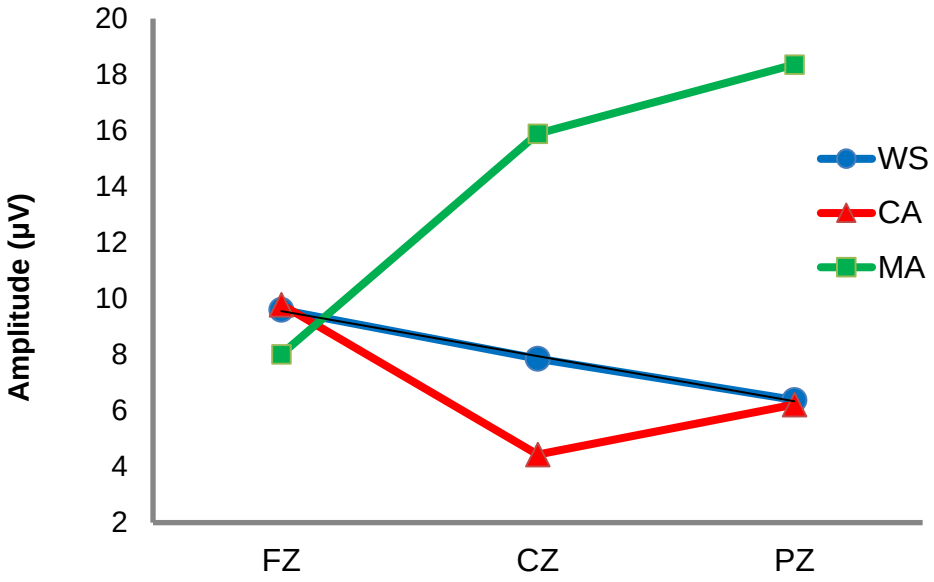


Figure 9: Mean P3b amplitude (μv) for the WS, CA, & MA groups at FZ, CZ, & PZ electrode sites

5.3.1.4 P3b latency

The ANOVA found no main effect of group [F(2,32) = 2.323, p=.114], a significant main effect of site [F(2,64) = 3.715, p=.03], and a significant Site x Group interaction [F(4,64) = 2.942, p=.027], on peak P3b latency. See Figure 10.

Site: Pairwise comparisons identified significantly faster P3b latency at FZ compared to CZ (p=.024) but not PZ (p=.679). The CZ/PZ comparison was non-significant (p=.456).

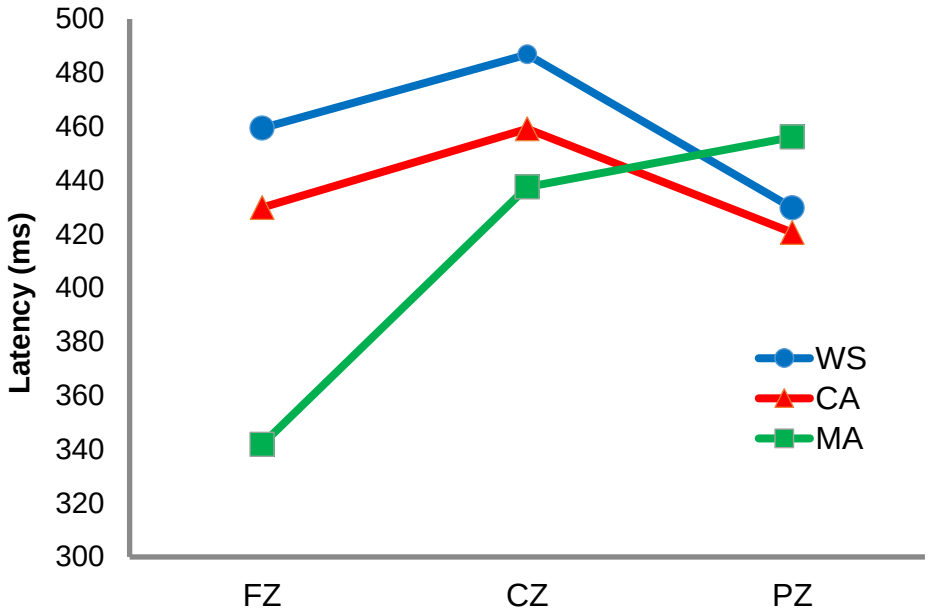


Figure 10: Mean P3b latency (ms) for the WS, CA, & MA groups at the FZ, CZ, & PZ electrode sites

*Site*group:* Independent t-tests revealed significantly greater peak P3b latency at FZ in the WS group compared with the MA group (p=.015) but not compared with the CA group (p=.242). Peak P3b latency was also significantly greater at FZ in the CA group compared with the MA group (p=.018). There were no group differences in peak P3b latency at CZ and PZ (all p≥.203). Paired samples t-tests revealed no differences in peak P3b latency between sites in the WS group (FZ/CZ, CZ/PZ, and FZ/PZ; all p≥.123). The CA group also showed no difference between FZ/PZ and CZ/PZ (p≥.144) In contrast, both the control groups' increase in latency from FZ to CZ approached significance (CA, p=.059; MA, p=.055). A significant increase in latency from FZ to PZ was also observed in the MA group (p=.027), but no latency difference between CZ and PZ (p=.582) (see Figure 11 for the P3b component headmaps).

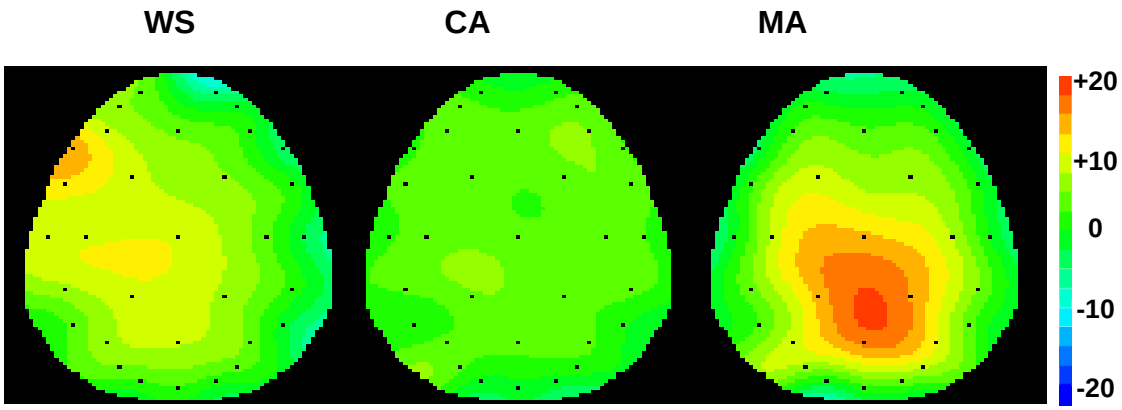


Figure 11: Headmaps for P3b component for the WS, CA, & MA groups

P3b summary: There was no difference in amplitude or latency between the WS and CA groups. The expected centro-parietal distribution, in both amplitude and latency, was only observed in the MA group, whereas the CA group presented a fronto-maximum. In contrast, no differences by site in P3b amplitude or latency were observed in the WS group.

5.3.2 Novel and target N2 results

The novel and target N2 amplitude and latency data were calculated from the mean of the raw peak amplitude and latency scores in response to the novel and target stimuli. Descriptive statistics for peak N2 amplitude and peak N2 latency to the novel and target stimuli are presented in Table 11 and Table 12.

Table 11: Mean peak amplitude (μv) and peak latency (ms) for the novel N2 (SDs in parentheses) for the WS, CA, & MA groups at FZ, CZ, & PZ electrode sites

	Amplitude			**Latency**		
	WS	CA	MA	WS	CA	MA
FZ	**-3.47** *(2.98)*	**-6.28** *(3.23)*	**-8.93** *(6.35)*	**251.05** *(42.69)*	**273.32** *(30.67)*	**260.83** *(42.17)*
CZ	**-4.91** *(6.44)*	**-10.79** *(7.19)*	**-2.16** *(7.59)*	**246.26** *(45.68)*	**258.67** *(41.49)*	**256.80** *(48.61)*
PZ	**-5.42** *(9.52)*	**-5.95** *(4.64)*	**-3.14** *(9.41)*	**219.31** *(21.14)*	**246.05** *(43.62)*	**221.44** *(17.25)*

5.3.2.1 Novel N2 amplitude

The ANOVA revealed no main effect of group [F(2,32) = 1.157, p=.327], or site [F(2,64) = .936, p=.398]. However, there was a significant Site x Group interaction [F(4,64) = 6.037, p<.001] on N2 amplitude to the novel stimulus.

*Site*group:* Independent samples t-tests identified significantly lower novel peak N2 amplitude at FZ in the WS group compared with both the CA (p=.045) and MA (p=.022) groups, but not between the control groups (p=.196). Greater novel peak N2 amplitude in the CA group at CZ approached significance compared with the WS group (p=.055), and was significantly greater than the MA group (p=.008). There were no differences in novel peak N2 amplitude at CZ between the WS/MA groups (p=.376) and no group differences at PZ (all p≥.347). Paired samples t-tests revealed no novel peak N2 amplitude differences by site in the WS group (FZ/CZ, CZ/PZ, FZ/PZ; all p≥.366). The CA group's peak amplitude was significantly greater at CZ compared with FZ (p=.017), and with PZ (p=.007), but there was no difference between FZ/PZ (p=.781). In contrast, the MA group

showed the opposite pattern with a significant decrease in novel peak N2 amplitude from FZ to CZ (p=.005) and FZ to PZ (p=.03), and no difference between CZ/PZ (p=.606) (see Figure 12).

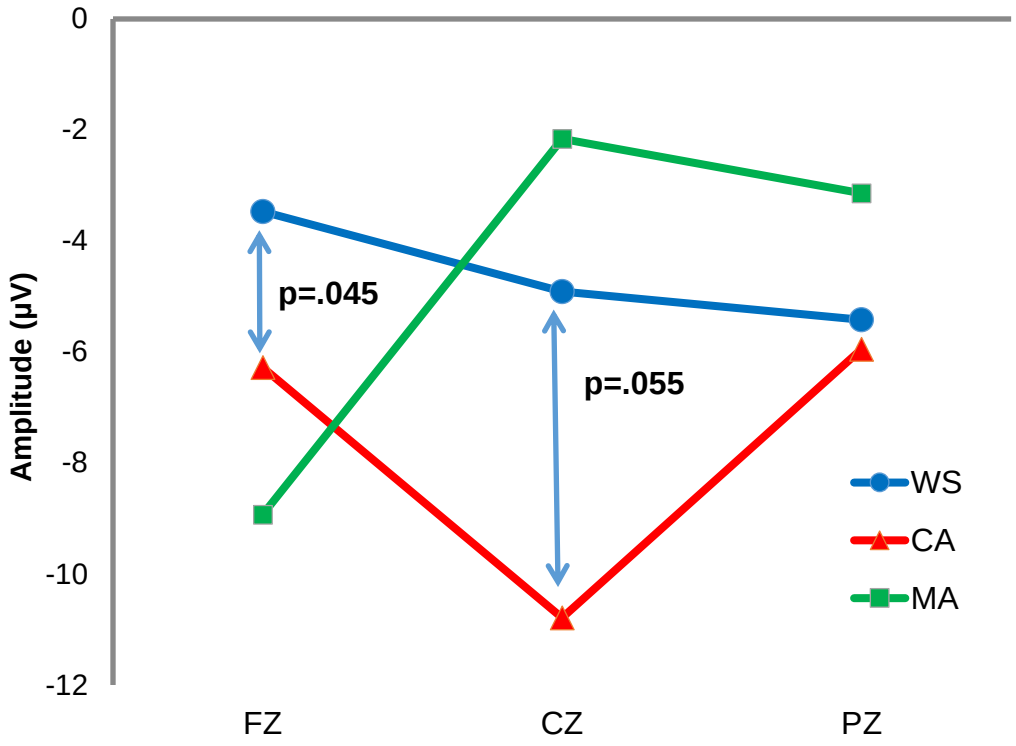


Figure 12: Mean peak N2 amplitude to the novel stimulus at FZ, CZ, & PZ for the WS, CA, & MA groups

5.3.2.2 Novel N2 latency

The ANOVA found no main effect of group [F(2,32) = 1.352, p=.273], a significant main effect of site [F(2,64) = 12.015, p<.001], and no Site x Group interaction [F(4,64) = .504, p=.733].

Site: Novel N2 latency was significantly faster at PZ compared to both FZ (p<.001) and CZ (p=.005).

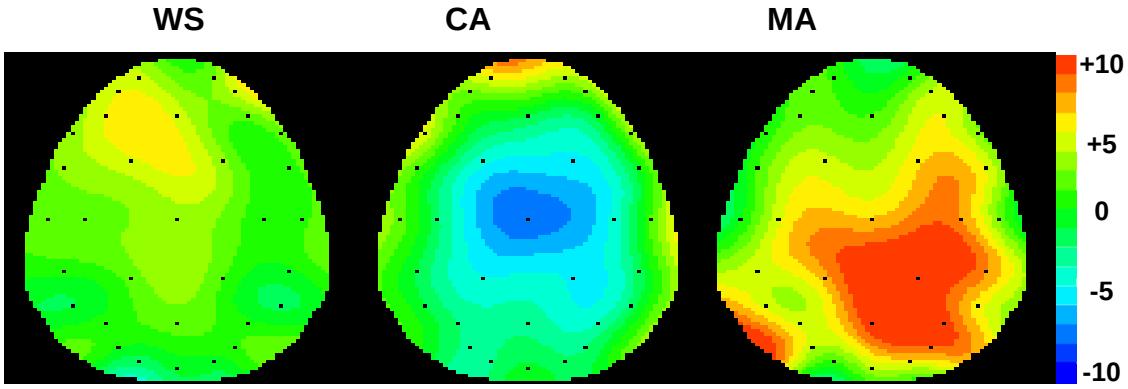


Figure 13: Headmaps for the novel N2 component for the WS, CA, & MA groups

Novel N2 summary: Group differences in topographic distribution were observed. The WS group presented no localised topographical distribution, and significantly attenuated FZ amplitude; whereas the CA group presented a central maximum and the MA group a frontal maximum. Faster parietal novel N2 latency was observed in all groups.

5.3.2.3 Target N2

Table 12: Mean peak amplitude (μv) and peak latency (ms) for the target N2 (SDs in parentheses) for the WS, CA, & MA groups at FZ, CZ, & PZ electrode sites

	Amplitude			**Latency**		
	WS	CA	MA	WS	CA	MA
FZ	**-2.87** *(2.74)*	**-4.79** *(4.76)*	**-7.93** *(4.94)*	**265.55** *(29.19)*	**266.63** *(48.43)*	**246.14** *(52.94)*
CZ	**-4.49** *(4.63)*	**-8.85** *(5.97)*	**-1.99** *(4.37)*	**279.46** *(33.02)*	**289.05** *(46.98)*	**223.68** *(43.73)*
PZ	**-4.20** *(6.41)*	**-3.27** *(4.48)*	**-0.26** *(6.68)*	**264.38** *(43.23)*	**260.28** *(54.63)*	**235.40** *(21.27)*

The mixed ANOVA found no significant main effect of group [F(2,32) = 1.033, p=.368], a significant main effect of site [F(2,64) = 5.382, p=.007], and a significant Site x Group interaction [F(4,64) = 7.698, p<.001], to target N2 amplitude.

Site: Pairwise comparisons revealed significantly attenuated target N2 amplitude at PZ compared to both FZ (p=.047) and CZ (p=.015), but no difference between FZ/CZ (p=1.00).

*Site*group:* Independent t-tests revealed significantly attenuated target peak N2 amplitude at FZ in the WS group compared with the MA group (p=.009) but not the CA group (p=.269), and no difference between the CA/MA groups (p=.119). In contrast, the numerically greater peak amplitude found in the CA group at CZ approached significance compared with the WS group (p=.070), and was

significantly greater than the MA group (p=.003). There was no peak target N2 amplitude difference at CZ between the WS/MA groups (p=.208) and at PZ for all three groups (p≥.176).

Paired samples t-tests found no differences by site in peak target N2 amplitude in the WS group across all sites (FZ/CZ, CZ/PZ, FZ/PZ; all p≥.234). The CA group showed a significant increase peak target N2 amplitude from FZ to CZ (p=.004), a decrease from CZ to PZ (p=.001), and no difference between FZ/PZ (p=.191). In contrast, the MA group showed a significant decrease in peak target N2 amplitude from both FZ to CZ (p=.008) and FZ to PZ (p=.004), but not CZ/PZ (p=.379) (see Figure 14).

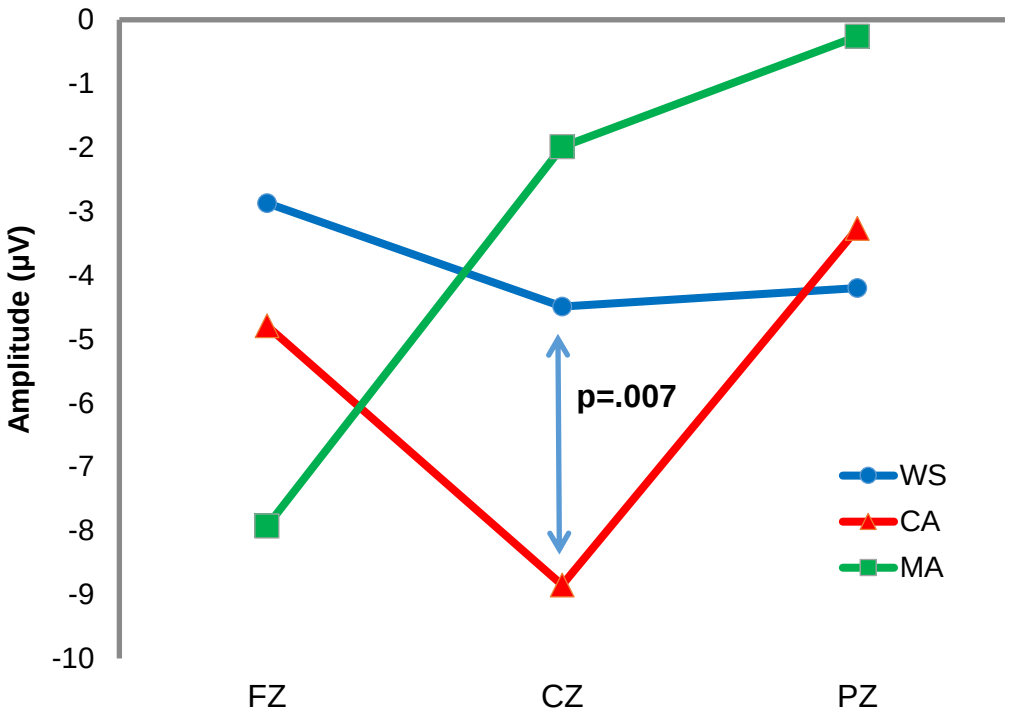


Figure 14: Mean N2 amplitude to target stimulus for the WS, CA, & MA groups at FZ, CZ, & PZ electrode sites

5.3.2.4 Target N2 latency

The analyses violated Mauchly's test of sphericity: therefore a Greenhouse-Geisser correction was applied. The mixed ANOVA revealed a significant main effect of group [F(2,32) = 5.246, p=.011], no significant main effect of site [F(1.662,53.173) = .726, p=.465], and no significant Site x Group interaction [F(3.323,53.173) = 1.500, p=.222], on target N2 latency.

Group: Tukey post-hoc comparisons revealed significantly faster peak target N2 latency in the MA group compared to both the WS (p=.037) and the CA (p=.016) groups. There was no difference in latency between the WS/CA groups (p=.985).

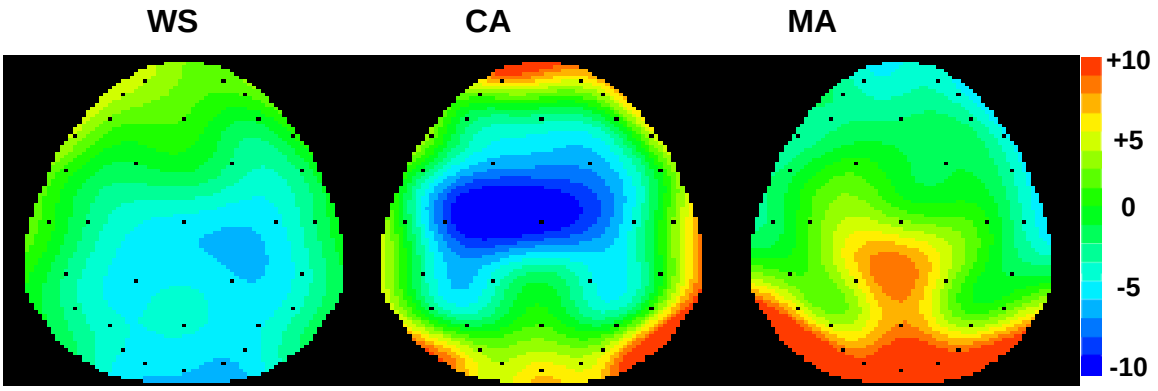


Figure 15: Headmaps for the N2 target component for the WS, CA, & MA groups

Target N2 summary: No localised topographical target N2 distribution was observed in the WS group; whereas a central maximum was observed in the CA group, and a frontal maximum in the MA group. Thre was no difference in latency

between the WS and CA groups, whereas MA latency was faster compared to both the WS and the CA groups.

5.3.3 Behavioural results

Behavioural RT was slower in the WS group (mean 500.65ms, SD 64.56) compared to both the CA (mean 422.38ms, SD 32.76), and the MA (mean 490.67ms, SD 59.54) groups. A one-way ANOVA was applied to the reaction time (RT) data to the target stimulus. There was a significant main effect of group [$F(2,32) = 7.855$, $p=.002$]. The WS group's RT to the target was significantly slower compared with the CA group ($p=.004$), but not the MA group ($p=.889$). The CA group's RT was also significantly faster than the MA group's ($p=.008$) showing an increase in speed with age as would be expected. Speed of processing in the WS group was comparable to their mental age. There was no difference in accuracy in response to the target, with all groups' performance reaching 100% accuracy. Also there was no significant correlation between behavioural RT and target N2 / P3b latency (all $p \geq .090$).

5.4 Discussion

Leading on from the previous chapters of the thesis identifying atypical EF processes of attention and inhibition in WS, the aim of the current study was to investigate the neuro-cognitive mechanisms engaged during the Oddball task in adults with WS as a measure of attentional and inhibitory control. To date, there is no known published research in the WS literature which has adopted the three-stimulus Oddball paradigm as used in the current study. The paradigm was

ideally suited to track different aspects of executive control and inhibition within one task. By utilising the strengths of ERPs the data contribute to understanding the behavioural profile exhibited by the disorder (e.g. disinhibition and disproportionate attention to social stimuli), this has provided a theoretical contribution of the atypicalities in these neural mechanisms. The results indicated atypicalities in earlier and later ERP components, and dissociation between involuntary and voluntary attentional processing. The main findings were as follows: compared to the CA group, the WS group's N2 peak amplitude was attenuated in response to the novel and target stimuli, P3a peak latency was increased in response the novel stimulus, but P3b peak amplitude or N2 / P3b peak latency did not differ in response to the target stimulus.

Focusing first on the P3a component related to orientation of attention and inhibition: the P3a amplitude was not particularly informative in terms of the WS group comparison with no significant difference in P3a amplitude between the WS and control groups irrespective of site; however inspection of the scalp distributions identified specific group differences. Consistent with previous research, both the WS and the CA groups presented larger peak amplitude fronto-centrally in response to the novel stimulus as expected (Polich, 2007; Wetzel, Schröger, & Widmann, 2013), whereas a centro-parietal distribution was observed in the MA group (Comerchero & Polich, 1999). Whilst this suggests that there is similar response to the distracting task-irrelevant stimuli across groups, inspection of the latency data provides alternative evidence regarding the inhibitory deficits in the WS population. The WS group displayed an overall delay in P3a peak latency, compared to both the CA and the MA groups. The amplitude

data may therefore be indicative of similar levels of attention during the 'automatic' shift in focus to the distracting novel stimulus, whereas the greater P3a latency is suggestive of longer and inefficient stimulus evaluation before switching back to the task at hand. This finding is consistent with the delayed P3a peak latency observed in younger adults with WS (Key & Dykens, 2011), and young–middle aged adults with FXS (Van der Molen, Van der Molen, Ridderinkhof, Hamel, Curfs, & Ramakers, 2012). As the amplitude of the P3a is thought to highlight the extent of involuntary shifts in attention (Escera, Yago, & Alho, 2001), the results indicate that adults in the WS group have the same neural responsivity to the novel stimulus as age-matched TD controls; therefore, their deficits in the disengagement from task-irrelevant information is evidenced by a delay in the neural mechanisms required to automatically detach from one task and refocus attention on an unexpected event. When applied to their behavioural profile, this suggests that inappropriate behavioural actions are likely linked to similar orientation of attention to irrelevant stimuli in the environment but less ability to disengage (see atypicalities of disengagement, but not engagement, to social information; Lincoln, Lai, & Jones, 2002; Riby & Hancock, 2009a; Riby et al., 2011). Considering evidence of attention disengagement difficulties in toddlers with WS (e.g. Brown et al., 2003), the current study emphasises that this is a difficulty that is exhibited across the developmental spectrum.

The results from the P3b data also highlighted an unusual neural profile, in both the adults with WS and the CA-matched group. Overall there were no significant differences in P3b peak amplitude between the WS and the CA adults; however the CA group presented a significant frontal maximum, whilst the MA

group presented an enhanced centro-parietal P3b distribution as expected (Thomas & Nelson, 1996). An anterior shift in P3b distribution is observed with increasing age in TD older individuals (~70+ years; Kopp, Lange, Howe, & Wessel, 2014), but has also been observed in middle-age (~49 years; Smit, Posthuma, Boomsma, & de Geus, 2007). This shift is thought to reflect an increasing age-associated reliance on frontally controlled executive processes during contextual updating, a process which is more automatic in younger individuals (Velanova, Lustig, Jacoby, & Buckner, 2007), and thus explains the frontal maximum observed in the CA group. In contrast, no significant differences in P3b peak amplitude were observed in the WS group across the three midline sites. The absence of any topographic P3b differences infers a less efficient voluntary attentional processing system to the task-relevant stimulus; alternatively it could reflect the recruitment of a wider range of cortical regions during voluntary attentional processing to compensate for the known abnormalities in WS such as reduced parietal grey matter density (Reiss et al., 2000), and disproportionate decrease in parietal volume (Chiang et al., 2007; also see Kim, 2014, for a meta-analysis on dorsal / ventral activity during Oddball paradigms in typical development).

Similarly, it was hypothesised that the WS group would demonstrate increased P3b latency, reflective of the WM impairments associated with the syndrome (Costanzo, Varuzza et al., 2013; Rhodes et al., 2011) and the deficits this group of adults with WS demonstrated in the WM tasks of general cognitive battery in Chapter 2. Combined with the P3b amplitude profile, the lack of any difference in P3b peak latency between the WS and the CA groups in the current

study suggests that the Oddball paradigm did not place great demands on WM processes and on sustained attention in our WS cohort, unlike the SART behavioural data which incorporated high *Go* / low *No-Go* methodology (Chapter 4). (For discussions on delineating different aspects of attention due to differences in the domains more or less impaired between syndromes, see Brown et al., 2003, and Cornish et al., 2007). Thus, the results indicate that, when targeted attention is required and under conditions that do not place great demands on WM and voluntary attentional processes, adults with WS are able to achieve the same behavioural result but through slightly different neural mechanisms (also see Lifshitz, Kilberg, & Vakil, 2016, for a meta-analysis on WM ability in developmental disorders). This result is also comparable with adults with ADHD (Barry, Clarke, McCarthy et al., 2009), but not younger individuals with ASD who present delayed P3b peak latency (Sokhadze et al., 2009).

The results from both the novel and target N2 component also contribute in elucidating atypicalities in the WS neural profile during involuntary and voluntary attentional processing. The WS group did not demonstrate any localised novel or target N2 distributions, evidence by non-significant differences in N2 peak amplitude across all three midline sites in both conditions. Furthermore, relative to both the CA and MA controls, significantly reduced frontal novel N2 peak amplitude was observed in the WS group; and, compared to the CA group, a reduction in both the novel and target N2 peak amplitude at the central site which approached significance. This contrasts with the limited published research documenting the N2 in WS which highlighted atypically enhanced N2 negativity in response to both upright and inverted faces (Mills et

al., 2000, 2013), and in response to repeated faces and houses (Key & Dykens, 2015). However, it is important to emphasise that WS is often associated with a pro-social drive and a fascination for looking at faces; therefore the results documented by Mills et al. (2000, 2013) may reflect the atypical neural profile that delineates their propensity for prolonged face gazing (Riby & Hancock, 2008) and not the executive deficits under investigation in the current programme of research. However also see behavioural studies by Riby et al. (2011) who found atypicalities in attentional disengagement was central to prolonged face gazing, and Little et al. (2013), who found impaired inhibition central to increased social approach. Thus the results from the N2 component here appear to support this behavioural evidence, though this needs to be substantiated with further ERP research employing these paradigms.

A final consideration with the current study relates to the handedness of the participants. Typically, electrophysiological research paradigms control for right-handedness due to differences in corpus callosal pathways (Luders et al., 2010). For example larger P300 amplitude and greater latencies have been observed in right-handed individuals (Eskikurt, Yücesir, & İsoglu-Alkac, 2013), though there have been conflicting results found also (Polich & Hoffman, 1998). Three of the WS group were left-handed but were included in the study due to the rarity of the disorder, and thus the small sample size. Informal dialogue with parents / carers supported the research which has highlighted a high proportion of left-handedness in WS compared with the typically developing population (Pérez-García, Flores, Brun-Gasca, & Pérez-Jurado, 2015; van Strien et al., 2005). Controlling for handedness may not be appropriate, as is commonplace in

the TD literature, as this would result in a sample unrepresentative of the syndrome. However, in WS research with larger sample sizes, it would be beneficial to compare the data between the right- and left-handed participants to identify if there are any differences in the ERP profile. This would be highly informative, especially as the increased ratio of left-handedness in WS has been linked to even greater reductions in corpus callosum volume compared with right-handed WS individuals (Martens, Wilson, Chen, Wood, & Reutens, 2013), and which may result in deficient inter-hemispherical communication.

In conclusion, the adults with WS presented an atypical delay in their involuntary attentional processes, most likely due to earlier perceptual processing deficits evidenced by the attenuated novel N2 amplitude. Deficits in the monitoring of task-relevant and irrelevant stimuli were comprised in WS at this early unconscious stage of processing. Their atypical N2 and P3b profile combined with their behavioural performance reaching ceiling level, indicated that they were able to overcome perceptual processing deficits in response to the target stimulus when more effortful voluntary processing was required. In contrast, the P3a latency in the present study appears to be key index and indicative of poor return to the processing of task relevant stimuli. The use of ERP methodology in the current study has added to our understanding the behavioural profile exhibited by individuals with WS (e.g. disinhibition and disproportionate attention to social stimuli), thus providing a theoretical contribution of the atypicalities in these neural mechanisms. The final empirical chapter will move on from these ERP findings by investigating the profile of the EEG alpha and beta

frequency bands during resting states, and the role these play in the attention and inhibitory atypicalites discussed throughout the thesis.

Chapter 6: Study 5 – Eyes Closed, Eyes Open, EEG Methodology

6.1 Introduction

It has been noted in the thesis, and elsewhere in the literature, that successful performance on behavioural tasks is influenced by the level of task difficulty (e.g. free-recall paradigms, Devenney et al., 2004, cf. semantically primed targets, Tyler et al., 1997). The group of adults with WS who participated in this programme of research demonstrated comparable performance with typical control groups when provided with greater levels of environmental support (Chapter 3, LoP) and under low task-demand conditions (Chapter 5, Oddball), but showed deficits in AM performance when task demands were notably greater (Chapter 2, AM; Chapter 4, SART). Chapter 5 (Oddball task) adopted an ERP methodology and has been informative in highlighting atypicalities in the ERP signature in adults with WS, linking this to known atypicalities of the behavioural and cognitive phenotype of the syndrome. However there are inconsistencies in the ERP literature, likely reflecting the recruitment of less impaired / spared cortical and subcortical regions in order to achieve the same behavioural result (e.g. ADHD, Prox et al., 2007; FXS, Menon et al., 2004). Certainly, it has been documented in many areas of functioning and across the WS developmental spectrum, that seemingly good performance might be achieved by 'different' routes and using different mechanisms (e.g. face perception; Karmiloff-Smith et

al., 2004). In light of this, the focus of this final empirical chapter was to investigate baseline cortical activity in the absence of goal-directed cognitive processing in adults with WS and compare this with typically developing CA-matched adults and MA-matched children. The central aim was to identify any differences in their resting-state neural signature which may underpin the attentional and inhibitory behavioural profile described in previous chapters. In order to provide a more comprehensive profile of neuropsychological processes in WS, the current study adopted electroencephalography (EEG) methodology in order to elucidate how cortical activity in the alpha and beta bands during resting states might be associated with the known behavioural and cognitive phenotypes.

6.1.1 Recap of the functional significance of the alpha and beta bands

The alpha band is primarily associated with attention, inhibitory processes, and the mechanisms of attention and consciousness (for a review, see Palva & Palva, 2007). As outlined in Chapter 1 (General Introduction, *section 1.2.5*), unlike the other frequency bands, alpha activity presents an inverse profile whereby an increase in alpha power (synchronisation) is indicative of less cortical activity, whilst a decrease in alpha power (desynchronisation) reflects activity in response to visual / sensory input (Bollimunta et al., 2011; Jensen et al., 2002; Klimesch, 2012; Klimesch et al., 2007). Increased alpha power is believed to reflect cortical inhibitory processes, whereas decreased alpha power reflects a release from cortical inhibitory control, enabling the recruitment of attentional resources in response to changing task demands (Haegens et al., 2011; von Stein et al., 2000). These patterns of synchronisation / desynchronisation are task-relevant (Haegens et al., 2010; Poliakov et al., 2014), and also have

functionally associated topographical distributions whereby decreases indicate activation in task-relevant cortical regions whilst simultaneous increases reflect the inhibition of task-irrelevant ones (Klimesch et al., 2007; Palva et al., 2010). Atypical patterns in alpha synchronisation / desynchronisation are functionally associated with impairments in cognitive processing. For example, during stimulus-response tasks such as the Oddball paradigm (Chapter 5), decreased alpha power prior to an upcoming *No-Go* stimulus signals a release from cortical inhibition thus enabling the cognitive processes required for inhibiting motor actions (De Blasio & Barry, 2013; Dockree et al., 2004). However, brief increases in pre-frontal and posterior pre-stimulus alpha power are associated with attentional lapses and poorer task performance (MacDonald et al., 2011; van Driel et al., 2012).

As highlighted in *section 1.2.6* of the General Introduction, the role of the beta band in top–down visual-attentional processing is widely documented (e.g. Gross et al., 2004; Kamiński et al., 2012; Seigel et al., 2012), and also has functionally distinct topographical distributions. Occipito-parietal beta power is associated with better performance on tasks which recruit attentional processes (e.g. Basile et al., 2007; Kamiński et al., 2012; MacLean et al., 2012), whereas diverted attention results in attenuated beta, even if a change in stimulus is expected (Todorivic et al., 2015). Increases and decreases in beta power are also functionally associated with the execution and inhibition of voluntary movements, with increased beta activity when voluntary movements are to be suppressed (Kühn et al., 2004; Zhang et al., 2008), and decreased beta activity during the preparation and execution of voluntary movements (Alegre et al., 2006;

Tzagarakis et al., 2010; Wheaton et al., 2009). Similar to the pattern observed in the alpha band, during response inhibition tasks, increased pre-stimulus beta power predicts successful inhibition in response to *No-Go* stimuli (Swann et al., 2009; Wheaton et al., 2009). In contrast, beta activity post-commission errors is characterised with greater rebound, indicative of increased response inhibition (Koelewijn et al., 2008).

6.1.2 Alpha and beta – atypical activity and developmental disorders

The functional roles of the alpha and beta bands have been identified in research with both human and non-human participants, and supported by behavioural deficits which can be linked to atypicalities in alpha and beta activity. For example, a recent study investigating age-associated differences in beta activity during a sustained attention task in TD adults (Gola et al., 2013) found no overall differences in beta power or task performance that could be attributed to increased age. Both younger (n=17, mean age 22yrs 4mths) and older adults (n=18, mean age 74yrs 10mths) displayed greater occipital beta power prior to correct responses, and also positive correlations between increased power and response accuracy; whereas erroneous responses were preceded by decreases in beta power. However, in a sub-group of lower performing elderly adults, identified by greater behavioural deficits in sustained attention, beta activity was significantly attenuated when more demanding attentional processing was required compared with the less challenging conditions, thus impaired task-specific beta synchronisation. Furthermore, alpha activity with greater task difficulty ws increased in this group, indicative of impaired task-specific alpha desynchronisation (O'Connell et al., 2009).

Inspection of the literature on developmental disorders and clinical populations supports the link between alpha / beta dysfunction and executive deficits. The EEG profile in ADHD is typically characterised by an enhanced theta / beta ratio, compared with TD individuals (for a meta-analysis see Arns et al., 2012). Notably, when individual fast wave alpha levels are accounted for, group differences in behavioural performance dissipate, emphasising the relevance of atypical alpha activity in both the EEG and behavioural profiles associated with ADHD (Lansbergen et al., 2011; Woltering et al., 2012). This was demonstrated during a continuous attention performance task (CPT), where adults with ADHD (n=38, mean age 45yrs 7mths) observed significantly attenuated frontal low-alpha power (8–10 Hz) and greater beta power compared with healthy age-matched controls (n=42, mean age 46yrs 6mths), indicative of increased cortical activity during sustained attention (Loo et al., 2009). Furthermore, despite comparable behavioural performance, low-alpha was attenuated for the duration of the task in the ADHD group, but gradually increased in the control group indicative of lesser reliance on the inhibitory function of alpha during sustained attention across time. Loo and colleagues (2009) also found significant correlations between frontal low-alpha and increased commission errors / decreased RT in their controls but not the ADHD adults, indicative of an association between increasing low-alpha and impulsive response profile in TD individuals. In contrast, only a significant negative correlation between increased beta power and decreased behavioural task variability was observed in the ADHD group.

In a separate CPT study, Hale et al. (2010) observed lateralisation differences with atypically enhanced parietal beta in ADHD adults (n=35, mean age 44yrs 7mths) in the right hemisphere, compared with left-lateralisation observed in age-matched controls (n=104, mean age 44yrs 8mths). Combined, these studies suggest a different EEG distribution between individuals with ADHD and TD controls during sustained attention. This methodology might identify atypical mechanisms underlying task performance in ADHD compared to those developing typically. Furthermore, chronic attenuated low-alpha and enhanced beta power in ADHD appears to be a compensatory mechanism, notably with increasing task demands, whereby this group require greater cortical activity to maintain sustained attention and reduce behavioural variability. This emphasises the need to include electrophysiological alongside behavioural paradigms in research with individuals with developmental disorders.

A similar profile in the alpha band was observed between healthy adults and clinical patients. Adopting a *Go / No-Go* paradigm, Roche et al. (2004) compared neural activity between a group of TBI adults (n=7, mean age 39yrs 6mths) and healthy age-matched controls (n=8, mean age 40yrs 0mths). They also found a positive correlation between alpha power and commission errors in control subjects, indicative of a functional association between increasing alpha power and task-disengagement in the healthy brain. However they found no comparable correlation in their clinical group despite making significantly more commission errors than the healthy controls. Roche and colleagues (2004) interpret this as an inability to maintain alpha desynchronisation, resulting in fluctuations in sustained attention and subsequent poorer response inhibition.

This emphasises behavioural deficits due to atypical alpha activity; however see Thomas and Karmiloff-Smith (2002) for a discussion of issues when comparing research evidence from developmental disorders and TBI individuals.

6.1.3 Resting states – Eyes Closed / Eyes Open

Thus far, the research discussed in this chapter has documented the role of the alpha and beta bands during goal-directed cognitive processing in the TD brain, developmental disorders, and clinical populations. However, as demonstrated in the thesis (LoP, Chapter 3 / Oddball, Chapter 5) and in the neurodevelopmental literature, under certain task conditions, atypically developing groups and clinical populations can perform as well as TD individuals (behaviourally). Thus, elucidating how and why the neural mechanisms and their associated behavioural processes differ between developmental disorders and typical development can be problematic. As electrophysiological activity whilst unconscious (i.e. during sleep / coma) and during resting states (i.e. relaxed conscious) have distinct profiles that can be dissociated from conscious sensory and cognitive processing (Cirelli & Tononi, 2015; Gosseries et al., 2014; Marzano et al., 2013), by studying neural activity in the absence of stimulus-induced / goal-directed activity, researchers can distinguish how cortical and subcortical processes differ between active and passive conditions.

Typically, resting-state activity is recorded by implementing Eyes Closed (EC; whereby participants rest with their eyes closed), and/or Eyes Open (EO; where they focus on a non-task-related visual stimulus) paradigms (see *section 1.2.8* of the General Introduction). During resting states, both alpha and beta

activity is synchronised, and typically distributed over parieto-occipital regions during EC (Chen et al., 2008). Importantly, EEG sub-bands have different EC profiles. Low-alpha has a more widespread topography across anterior–posterior regions, whereas upper-alpha and beta are dominant posteriorly. Opening the eyes results in topographic changes; both alpha and beta bands demonstrate attenuated power; however the decreases in posterior regions are more pronounced in alpha, whereas beta is characterised by smaller posterior decreases and pre-frontal increases, believed to be the engagement of frontally controlled regions responsible for executive processes (Barry et al., 2007; Chen et al., 2008; Klimesch et al., 2007; Mantini et al., 2007). Research with developmental disorders highlights atypicalities in the resting-state EEG profile. For example, during five minutes of EC, Babiloni et al. (2009) observed significantly attenuated alpha, beta, and gamma in adolescents with DS (n=38; mean age 18yrs 8mths) and a TD age-matched control group (n=17, mean = 19yrs 1mth). Woltering et al. (2012) found attenuated alpha power in ADHD compared to controls during both EC and EO, whilst attenuated beta is widely acknowledged in the atypical theta / beta ratio (Arns et al., 2012). Beta power in FXS and controls is comparable, but FXS present significantly attenuated upper-alpha during EC (Van der Molen & Van der Molen, 2013), and is linked to executive dysfunction such as attentional lapses (cf. WS; Mobbs, Eckert, Mills et al., 2007). However there are mixed findings in the EEG resting-state profile in ASD (for a review, see Wang et al., 2013).

6.1.4 EEG profile in Williams syndrome

In the WS literature, the focus on neuroimaging methods such as fMRI and EEG is notably lacking compared to other developmental disorders such as ASD and ADHD. However, from the available EEG research, it would appear that an atypical EEG profile is present in WS under certain conditions, and which is in line with other developmental disorders (Bernardino et al., 2013; Bódizs et al., 2012, 2014; Grice et al., 2001; Lense et al., 2014). To date there is only one known study which specifically focuses on the EEG signature in WS during resting states. Ng, Fishman, and Bellugi (2015) investigated the profile of the alpha band in an EC / EO paradigm in a cohort of adults with WS adult (n=9, mean age 31yrs 4mths) and a group of TD adults (n=16, mean age 20yrs 8mths); the latter was sub-divided into a TD group and those who scored high on levels of extraversion. Of specific interest to the authors were frontal inter-hemispherical resting-state differences which might underpin the disinhibited social profile associated with WS. The WS group was characterised by attenuated frontal alpha power in the left hemisphere compared with both control groups, but no group differences in the right hemisphere. Notably, the WS and TD groups also demonstrated an opposite pattern of intra-hemispheric asymmetry. Greater right over left hemispherical asymmetry was observed in the WS group, whereas greater left over right asymmetry was observed in both the TD and extravert controls. Ng and colleagues (2015) functionally associate the over-recruitment of the left hemisphere in their WS group with neuropsychological profile including exaggerated anxieties associated with the syndrome (Dykens, 2003; Klein-Tasman & Mervis, 2003). There are notable methodological issues with this study due to the combining of the EC and EO data, thus interpretation of Ng et al.'s

(2015) study needs to be addressed with caution. However, their study is highly pertinent to the current programme of research, as the under-recruitment of the right frontal hemisphere in the WS group provides preliminary evidence for atypical baseline activity during resting states in WS in the cortical regions functionally associated with inhibitory processes (but also see Hampshire, 2015).

6.1.5 Hypotheses

The aim of this final empirical chapter was to characterise the alpha and beta band EEG profile in adults with WS during Eyes Closed and Eyes Open resting states. The three groups that made up the participants for this study were as those who participated in the Oddball study (Chapter 5) (WS, CA, & MA). In light of the dearth of EEG research with WS, hypotheses have been primarily guided by the ADHD research due to the neurocognitive similarities highlighted here and elsewhere in the thesis. It was hypothesised that adults with WS would present overall attenuated alpha (full alpha and both sub-bands) compared to the controls in both conditions, reflective of the suggested state of hyper-cortical arousal as found in ADHD. Attenuated beta power in WS was also hypothesised in both conditions, reflective of the attentional deficits observed in their behavioural profile. Overall greater power across all frequencies of interest was hypothesised in the MA group's EEG profile reflecting their developmental maturation.

6.2 Method

6.2.1 Participants

The participants for this study were the same as recruited for Chapter 5 (Oddball study – please refer to *section 5.2.1* for demographic details). From these groups, data from two of the WS group, three from the CA group, and three from the MA group were excluded due to EEG artefacts which compromised further analysis. Thus the final sample consisted of nine adults with WS, thirteen adults matched for chronological age (CA), and ten children matched for verbal mental ability (MA).

6.2.2 Physiological recording

Physiological recording took place during the same session as the Oddball task (see Chapter 5 *sections 5.2.2 - 5.2.4* for details). Participants completed the EC/EO task first. Power estimates were derived from the average for low-alpha (8–10 Hz), upper-alpha (10–12.5 Hz), and beta (13–29.5 Hz) frequency bands at frontal (F3, FZ, F4), central (C3, CZ, C4), and parietal (P3, PZ, P4), and occipital (O1, OZ, O2) sites (see Loo et al., 2009).

6.2.3 Procedure

Consent to participate and application of the EEG data recording equipment was as per Chapter 5. The participants were advised they would be required to sit still with their eyes closed for 2 minutes, then sit still with their eyes open for a further 2 minutes. During both conditions, the participants were asked to remain relaxed and silent, avoid head and body movements, and refrain from

blinking if possible. During the Eyes Open procedure, the participants were instructed to focus on a neutral spot straight ahead of them, and avoid eye movements for the duration of the task.

6.2.4 Data extraction

Post-acquisition processing was undertaken as per Chapter 5. The EEG data from each 2-minute segment were divided into 2-second epochs. Each epoch was subject to visual inspection and any epochs containing artefacts such as eye movements and blinks were manually rejected. For each subject in both conditions, average power spectra were calculated using Fast Fourier Transforms. At each electrode, absolute power in full alpha (8–12 Hz), low-alpha (8–10 Hz), upper-alpha (10–12.5 Hz) and the beta (13–29.5 Hz) bands were calculated.

6.3 Results

Summary data are presented in Appendices *iv* and *v*.

6.3.1 Eyes Closed

A 3 (group: WS / CA / MA) x 4 (location: frontal / central / parietal / occipital) x 3 (hemisphere: left / midline / right) mixed design Analysis of Variance (ANOVA) was applied to the data; with location and hemisphere as the within subjects factors, and groups as the between subjects factor. The ANOVA was applied to the following frequencies a: alpha (*α-full*), 8–12.5 Hz, b: lower-alpha (*α-low*), 8–10 Hz, c: upper-alpha (*α-high)*, 10–12.5 Hz, and d: beta (β), 13–29.5 Hz. Where

Mauchly's test of sphericity was significantly violated a Greenhouse-Geisser correction was used. Tukey and pairwise comparisons were employed to analyse significant main and interaction effects.

6.3.1.1 Alpha band (α-full) – 8–12.5 Hz

The ANOVA identified significant main effects of Group [F(2,31) = 5.466, p=.009], and Location [F(1.458,45.191) = 18.233, p<.001], on *α-full* power. A main effect hemisphere approached significance [F(1.216,37.681) = 3.399, p=.066]. Significant interactions between location and group [F(2.916,45.191) = 4.912, p=.005], and hemisphere by location [F(1.242,38.505) = 5.657, p=.017] were also observed. All other interactions were non-significant (p≥.132). See Figures 16 and 17.

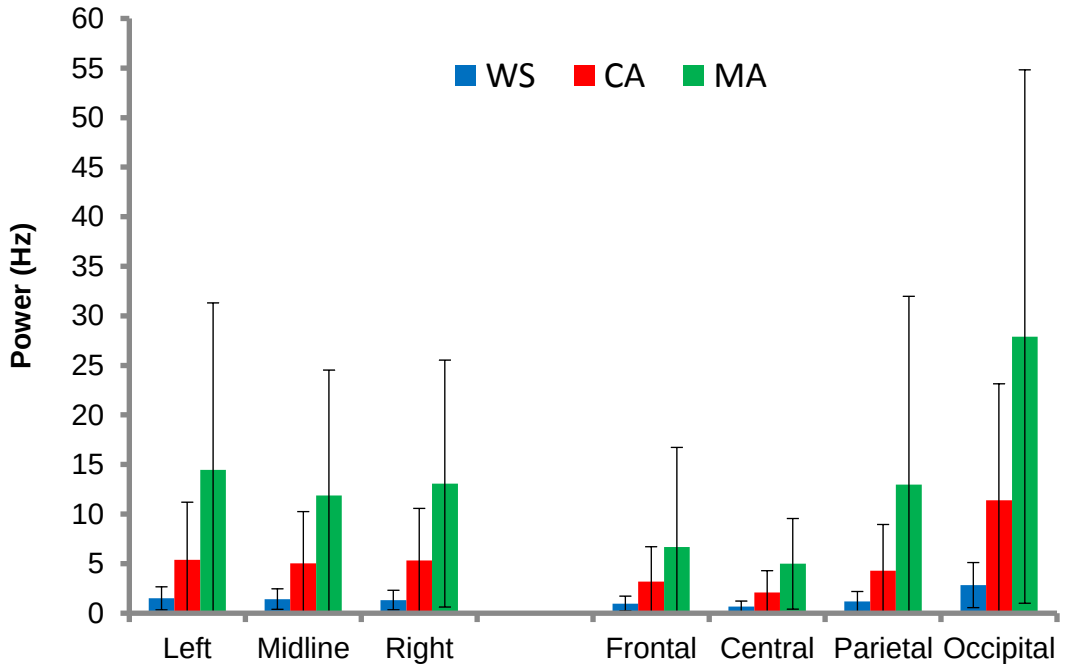


Figure 16: Mean absolute full-alpha power (Hz) for the WS, CA, & MA groups by hemisphere and location in the Eyes Closed condition. Error bars represent SDs

Group: Tukey post-hoc comparisons identified significantly lower *α-full* power in WS compared with MA group (p=.008), whilst the numerically lower *α-full* power in the CA group approached significance compared to the MA group (p=.075). There was no difference in *α-full* power between the WS and the CA groups (p=.502).

Location: Pairwise comparisons identified significantly greater occipital *α-full* power compared with the frontal, central and parietal locations (all p<.001). Parietal *α-full* power was significantly greater than the frontal (p=.007) and central (p=.016) locations. The difference in *α-full* power between frontal and central locations approached significance (p=.073).

Hemisphere: Pairwise comparisons identified lateralised distribution with significantly greater *α-full* power at the left (p=.024) and right (p=.015) hemispheres compared with midline. There was no difference in *α-full* power between the left and right hemispheres (p=.276).

*Location*group:* A one-way ANOVA revealed significant group differences in *α-full* power at central [F(2,31) = 6.239, p=.005], parietal [F(2,31) = 3.436, p=.045], and occipital [F(2,31) = 6.380, p=.005] locations, dominated primarily by greater power in the MA group. Post-hoc analyses revealed significantly greater *α-full* power in the MA than the WS group at the central (p=.004), parietal (p=.042), and occipital (p=.004) locations, and numerically greater *α-full* power in the MA group which approached significance compared with the CA group at the central (p=.055) and occipital (p=.056) locations. There was no difference in *α-full* power

at the frontal location across all groups (all p values ≥.080), and no group difference between the WS and CA groups across all locations (all p values ≥.450).

*Hemisphere*location:* This interaction was due to significantly attenuated frontal and central *α-full* power compared with hemispheric *α-full* power (all p≤.003). In contrast, occipital *α-full* power was significantly greater than observed at the left, midline, and right sites (all p<.001). There were no differences in *α-full* power by hemisphere at the parietal location.

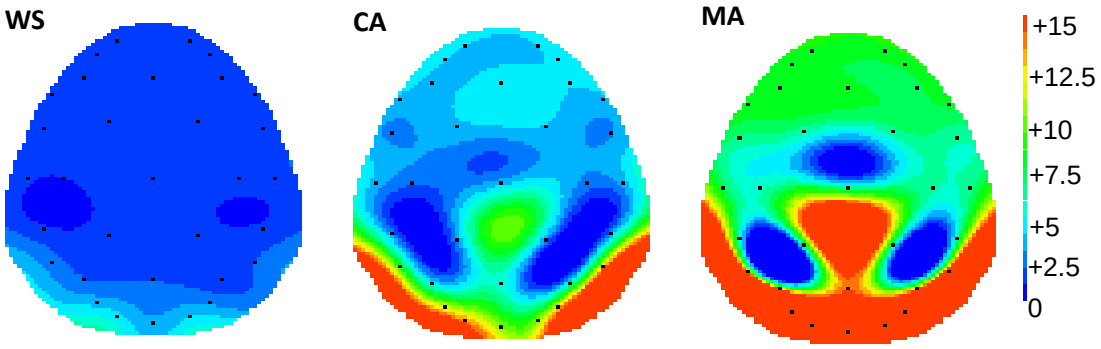


Figure 17: Spectral mapping of the full alpha band in the Eyes Closed condition for the WS, CA, & MA groups

6.3.1.2 Lower-alpha band (α-low) – 8–10 Hz

The ANOVA revealed significant main effects of group [F(2,31) = 4.754, p=.016], and location [F(1.615,50.061) = 22.671, p<.001] on *α-low* power, but not by hemisphere [F(1.553,48.150) = 2.778, p=.085]. Significant interactions of Location x Group [F(3.230,50.061) = 4.239, p=.008], and Location x Hemisphere

[F(1.527,47.324) = 6.452, p=.006] were observed, but not for Hemisphere x Group [F(3.106,48.150) = .973, p=.416]. See Figures 18 and 19.

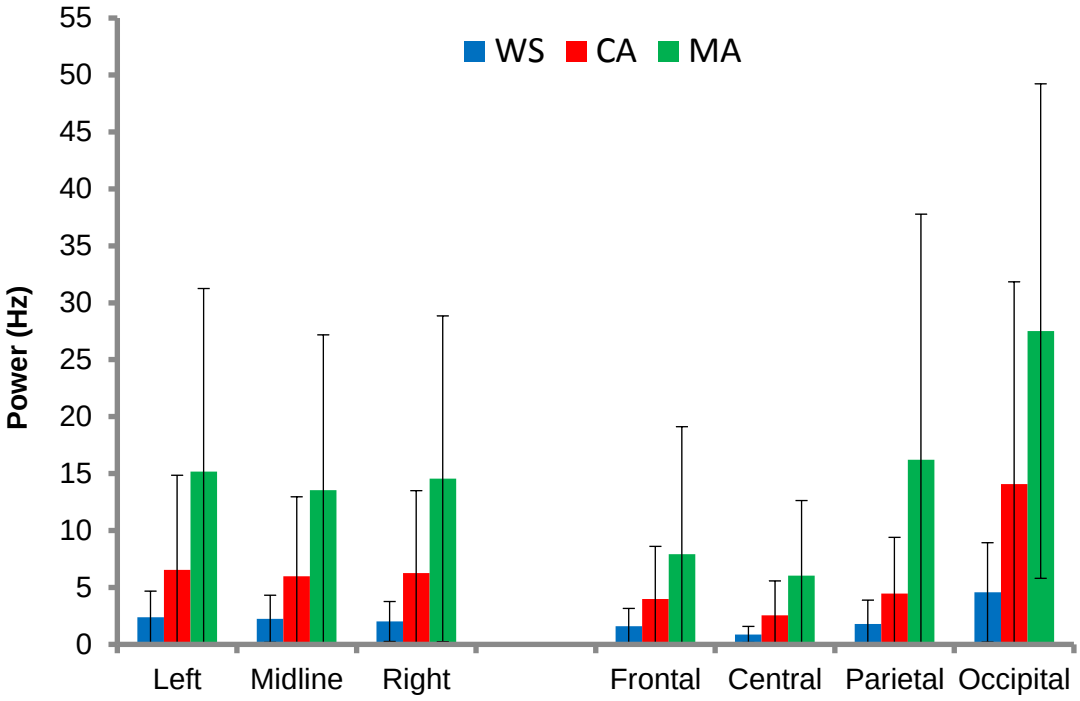


Figure 18: Mean absolute low-alpha power (Hz) for the WS, CA, & MA groups by hemisphere and location in the Eyes Closed condition. Error bars represent SDs

Group: Tukey post-hoc comparisons revealed significantly attenuated *α-low* power in the WS group compared with the MA group (p=.013), but no difference between the WS / CA (p=.536) and the CA / MA (p=.105) groups.

Location: Pairwise comparisons revealed significantly greater occipital *α-low* power compared with frontal, central, and parietal locations (all p<.001). Parietal *α-low* power was also significantly greater than observed frontally (p=.006) and

centrally (p=.005). Frontal *α-low* power was significantly greater than central (p=.011).

Hemisphere: Pairwise comparisons identified significantly greater *α-low* power in the left hemisphere compared with midline (p=.024). There was no difference in *α-low* power between left / right (p=.287) and midline / right (p=.169) hemispheres.

*Location*group:* A one-way ANOVA revealed group differences in *α-low* power at central [F(2,31) = 4.472, p=.020], parietal [F(2,31) = 4.216, p=.024], and occipital [F(2,31) = 5.219, p=.011] locations. Tukey post-hoc comparisons revealed group differences were due to significantly lower *α-low* power in the WS group compared to the MA group centrally (p=.016), parietally (p=.027), and occipitally (p=.008). Numerically lower parietal *α-low* power in the CA group compared with the MA group approached significance (p=.069). All other analyses were non-significant (p≥.095), notably there were no differences between the WS and the CA groups across all locations.

*Location*hemisphere:* Again, this interaction effect was due to significantly attenuated frontal and central *α-low* power compared with *α-low* power in all hemispheres (all p<.001), whilst occipital *α-low* power was significantly greater than observed by hemisphere (all p<.001). There was no difference in *α-low* power by hemisphere observed in the parietal location (all p≥.419).

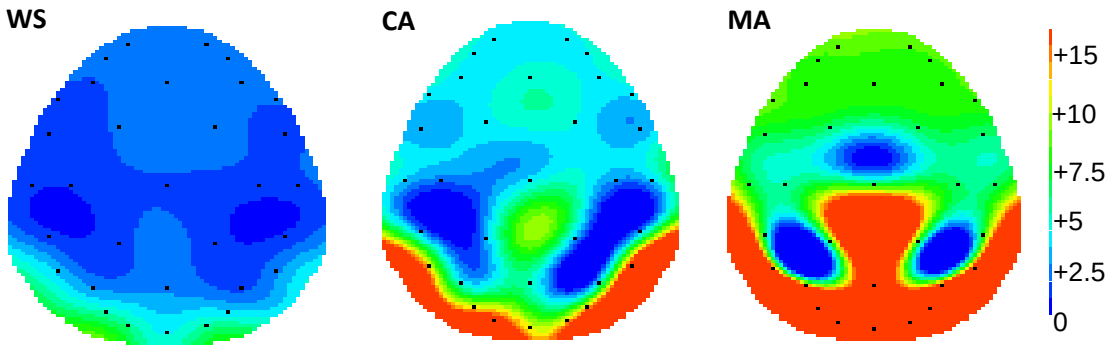


Figure 19: Spectral mapping of the lower-alpha band in the Eyes Closed condition for the WS, CA, & MA groups

6.3.1.3 Upper-alpha band (α-high) – 10–12.5 Hz

The ANOVA revealed significant main effects of group [F(2,31) = 4.993, p=.013], and location [F(1.275,39.523) = 10.435, p=.001], but not for hemisphere [F(1.151,35.674) = 2.609, p=.111], on *α-high* power. There were also significant interactions of location by group [F(2.550,39.523) = 3.977, p=.019], and location by hemisphere [F(1.252,38.823) = 3.985, p=.044]. See Figures 20 and 21.

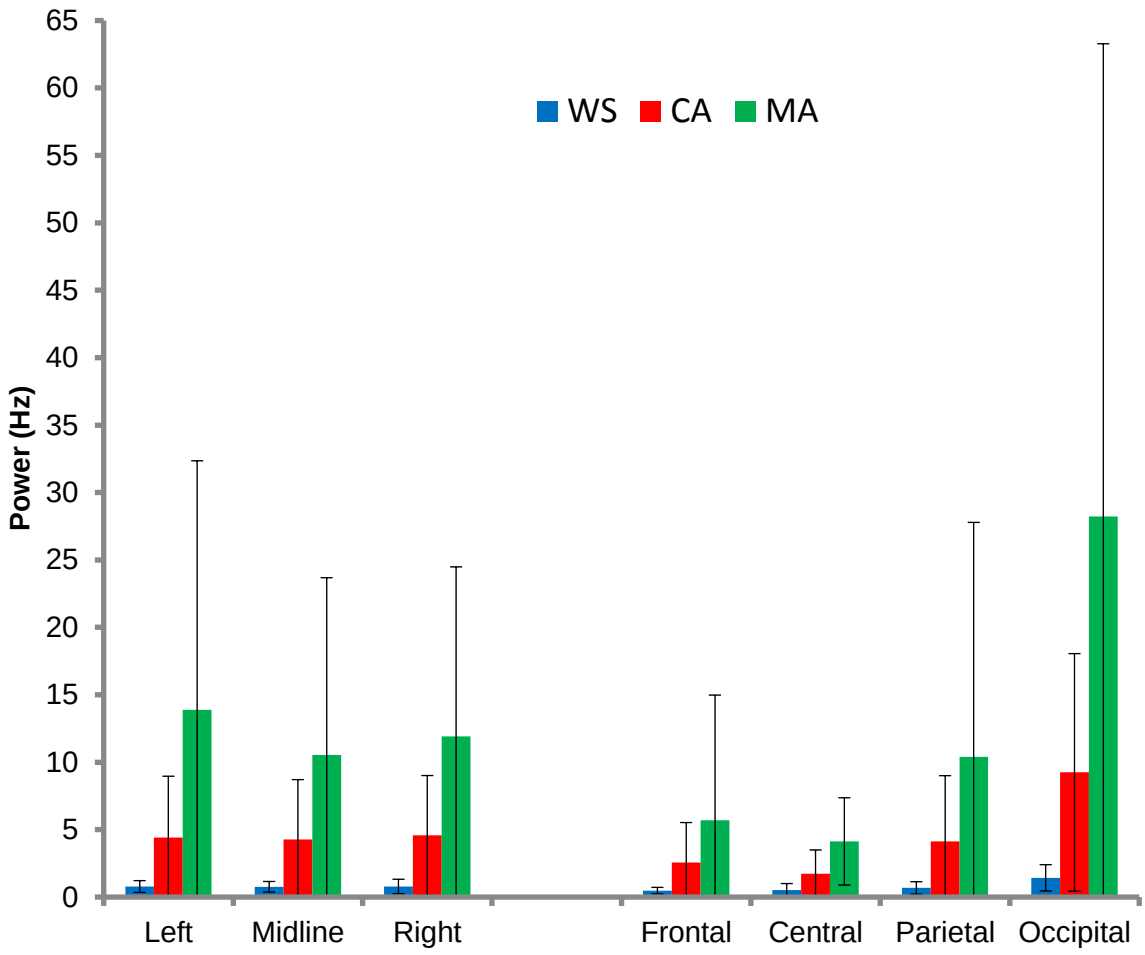


Figure 20: Mean absolute upper-alpha power (Hz) in the WS, MA, & CA groups by hemisphere and location in the Eyes Closed condition. Error bars represent SDs

Group: Tukey post-hoc comparisons revealed significantly lower *α-high* power in the WS group compared with the MA group (p=.011). Numerically greater *α-high* power in the MA group approached significance compared with the CA group (p=.089), but there were no group differences between the WS and the CA groups (p=.543).

Location: Pairwise comparisons revealed significantly greater occipital *α-high* power compared with the frontal (p=.001), central (p= .002), and parietal (p=.006) locations. Parietal *α-high* power was significantly greater than observed frontally

(p=.012) and centrally (p=.045). There was no difference in *α-high* power between frontal and central locations (p=.221).

*Location*group:* A one-way ANOVA revealed significant group effects at the central [F(2,31) = 8.104, p=.001], and occipital [F(2,31) = 5.117, p=.012] locations only. Tukey post-hoc comparisons revealed significantly greater central *α-high* power in the MA group compared with both the WS (p=.001) and CA (p=.027) groups. Occipital *α-high* power was also significantly greater in the MA group compared with the WS group (p=.011) and approached significance compared with the CA group (p=.072). There were no differences between the WS / CA groups either centrally (p=.346) or occipitally (p=.601).

*Location*hemisphere:* Paired samples t-tests revealed significantly attenuated *α-high* power at frontal location compared with the left (p=.006), midline (p=.005), and right (p=.002) hemispheres. Central *α-high* power was also significantly attenuated compared with the left (p=.016), midline (p=.010), and right (p=.003) hemispheres. In contrast *α-high* power was significantly greater in the occipital location compared with the left (p=.007), midline, (p=.005), and right (p=.008) hemispheres. There was no difference in *α-high* power between the parietal location by hemisphere (p≥.125).

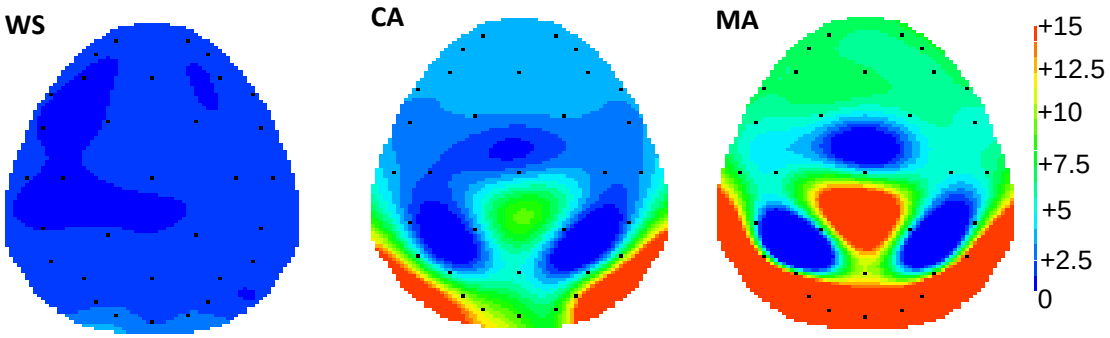


Figure 21: Spectral mapping of the upper-alpha band in the Eyes Closed condition for the WS, CA, & MA groups

6.3.1.4 Beta band (β) – 13–29.5 Hz

The ANOVA revealed a significant main effect of location on β power [F(1.356,42.042) = 5.781, p=.013], but no main effect of group [F(2,31) = 1.974, p=.156], or hemisphere [F(1.036,32.128) = 1.198, p=.284]. There were no significant interaction effects of group by location (all p values ≥.209). See Figures 22 and 23.

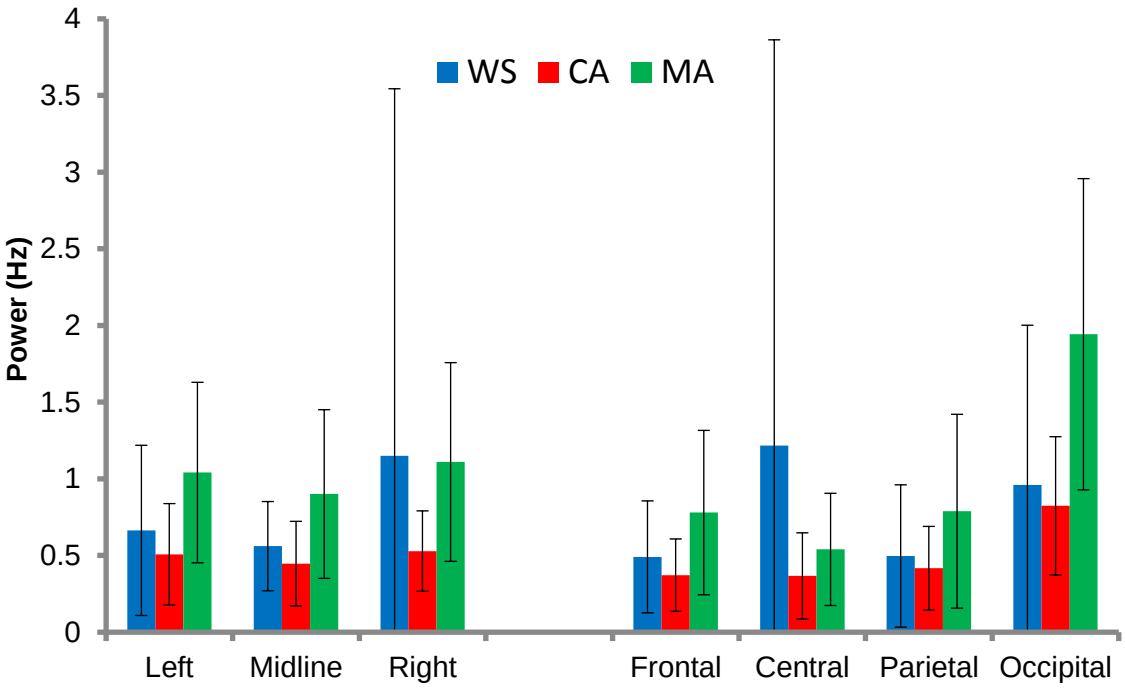


Figure 22: Mean absolute beta power (Hz) in the WS, CA, & MA groups by hemisphere and location in the Eyes Closed condition. Error bars represent SDs

Location: Pairwise comparisons revealed significantly greater occipital β power compared with the frontal and parietal locations (both p<.001), and numerically greater β power which approached significance compared with the central location (p=.076). All other comparisons were non-significant (p≥.489).

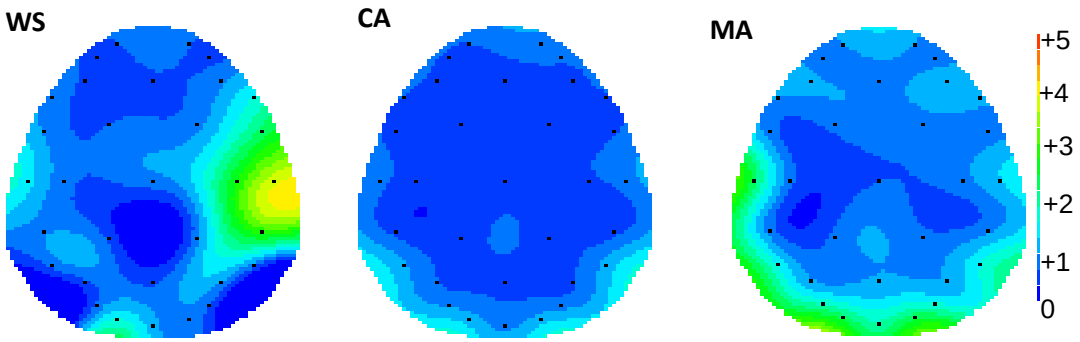


Figure 23: Spectral mapping of the beta band in the Eyes Closed condition for the WS, CA, & MA groups

6.3.2 Eyes Open

Statistical techniques for the Eyes Open condition were as per the Eyes Closed condition.

6.3.2.1 Alpha band (α-full) – 8–12.5Hz

Analyses identified significant main effects of group [F(2,31) = 3.930, p=.030], and location [F(1.369,42.432) = 10.444, p=.001], but not for hemisphere [F(1.323,41.017) = 1.465, p=.240] on *α-full* power. All interaction analyses were non-significant (p≥.088). See Figures 24 and 25.

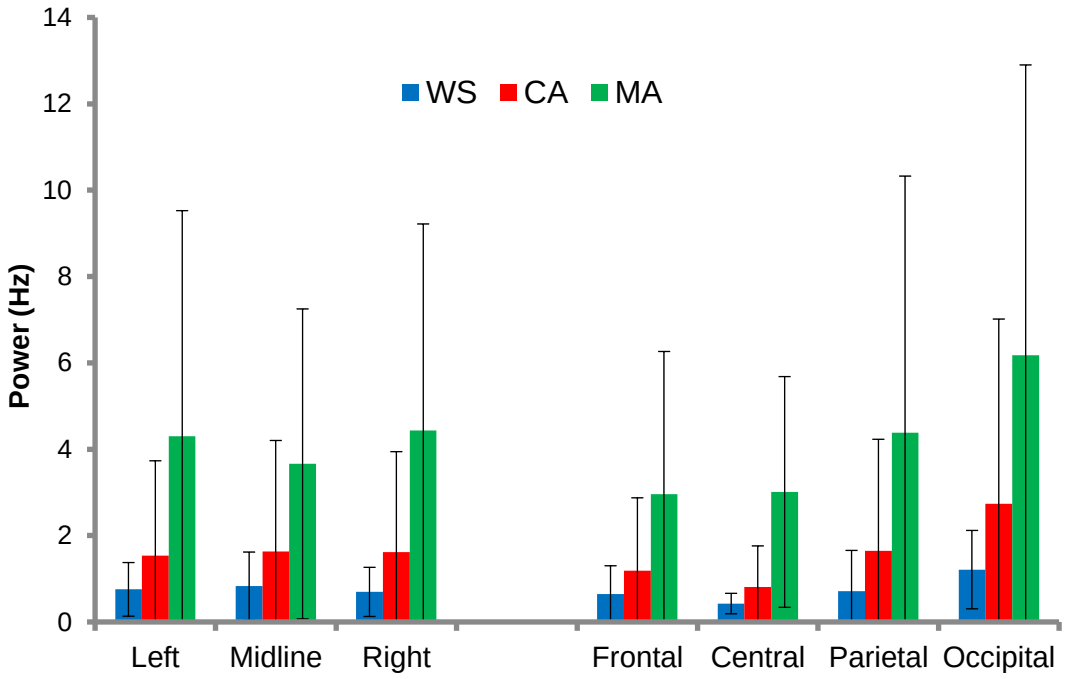


Figure 24: Mean absolute full-alpha power (Hz) in the WS, CA, & MA groups by hemisphere and location in the Eyes Open condition. Error bars represent SDs

Group: Tukey post-hoc comparisons identified significantly greater *α-full* power in the MA group compared with the WS group (p=.029), but no difference in *α-full* power between the WS / CA (p=.754) and CA / MA (p=.105) groups.

Location: Pairwise comparisons identified significantly greater occipital *α-full* power compared with the frontal (p=.001), central (p=.002), and parietal (p=.002) locations. Parietal *α-full* power was significantly greater than frontal (p=.025) and central (p=.037). There was no difference in *α-full* power between frontal and central locations (p=.262).

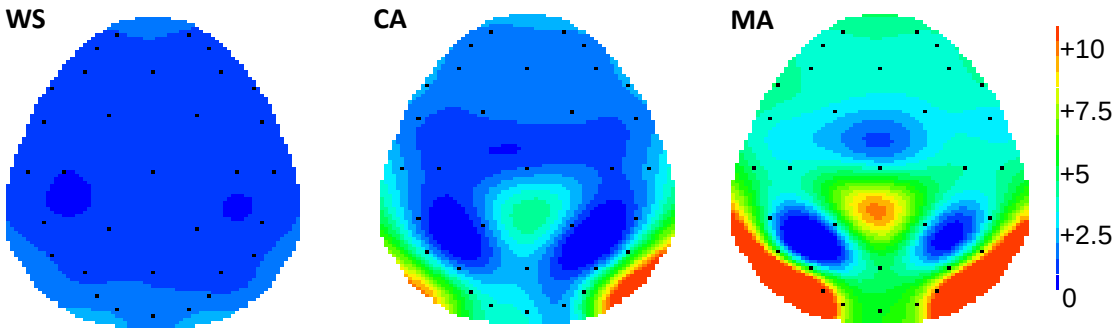


Figure 25: Spectral mapping of the full-alpha band in Eyes Open condition in the WS, CA, & MA groups

6.3.2.2 Lower-alpha band (α-low) – 8–10 Hz

The ANOVA identified significant main effects of group [F(2,31) = 3.860, p=.032], and location [F(2.140,66.351) = 8.705, p<.001], on *α-low* power, but not for hemisphere [F(1.331,41.250) = .394, p=.593]. All interaction analyses were non-significant (p≥.194). See Figures 26 and 27.

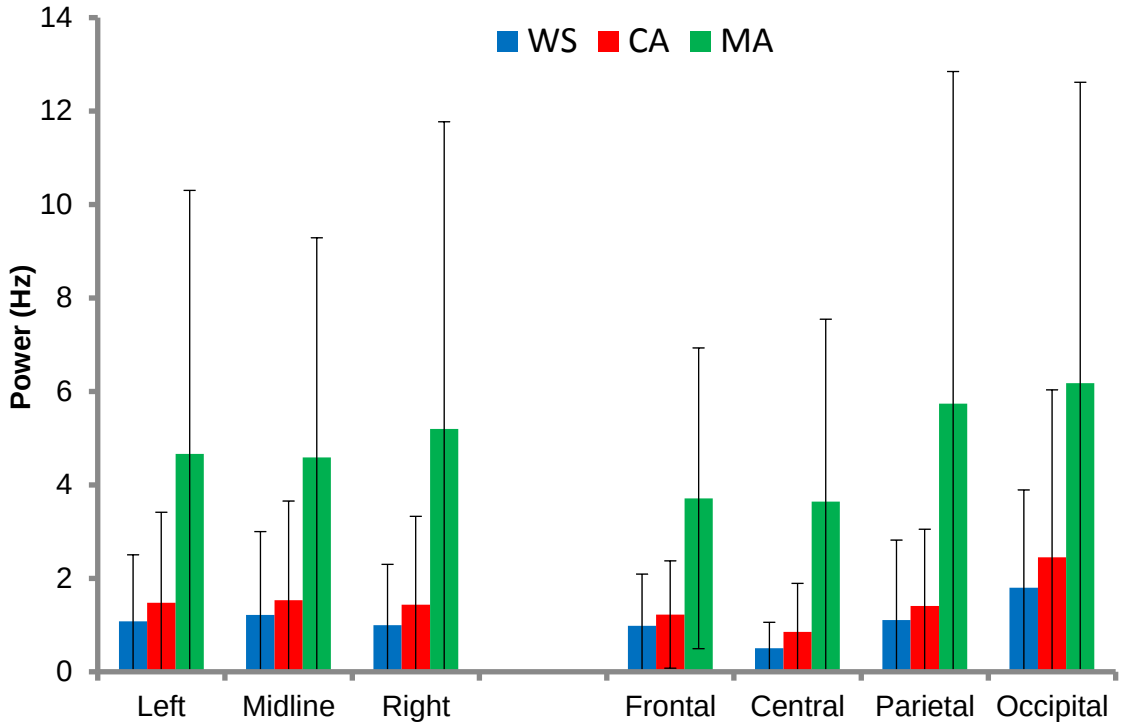


Figure 26: Mean absolute low-alpha power (Hz) in the WS, CA, & MA groups by hemisphere and location in the Eyes Open condition. Error bars represent SDs

Group: Tukey post-hoc comparisons revealed significantly greater *α-low* power in the MA group compared to the WS group (p=.044), and approached significance compared to the CA group (p=.064). There was no difference in *α-low* power between the WS and CA groups (p=.958).

Location: Pairwise comparisons revealed significantly greater occipital *α-low* power compared with both frontal and central locations (both p<.001) but not with parietal location (p=.090). Parietal *α-low* power was significantly greater than central (p=.017) location, and numerically greater than frontal (p=.071). There was no difference in *α-low* power between the frontal / central locations (p=.110).

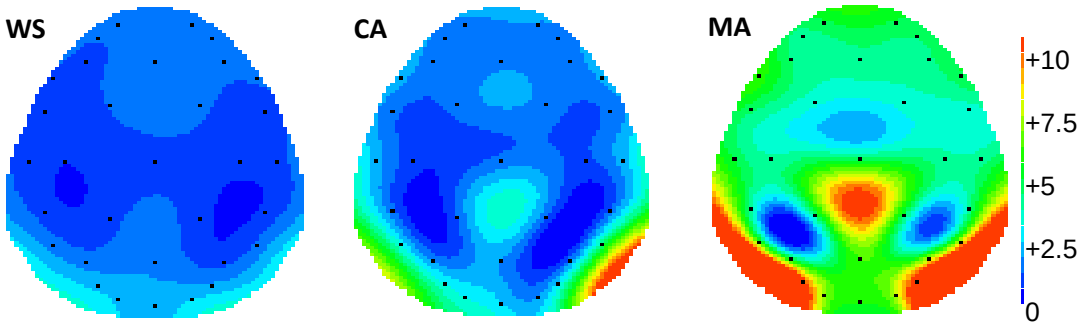


Figure 27: Spectral mapping of the lower-alpha band in the Eyes Open condition in the WS, CA, & MA groups

6.3.2.3 Upper-alpha band (α-high) – 10–12.5 Hz

The ANOVA identified significant main effects of group [F(2,31) = 3.788, p=.034], and location [F(1.123,34.799) = 9.556, p=.003], but not for hemisphere [F(1.240,38.446) = 2.137, p=.148]. All interactions were non-significant (p≥.129). See Figures 28 and 29.

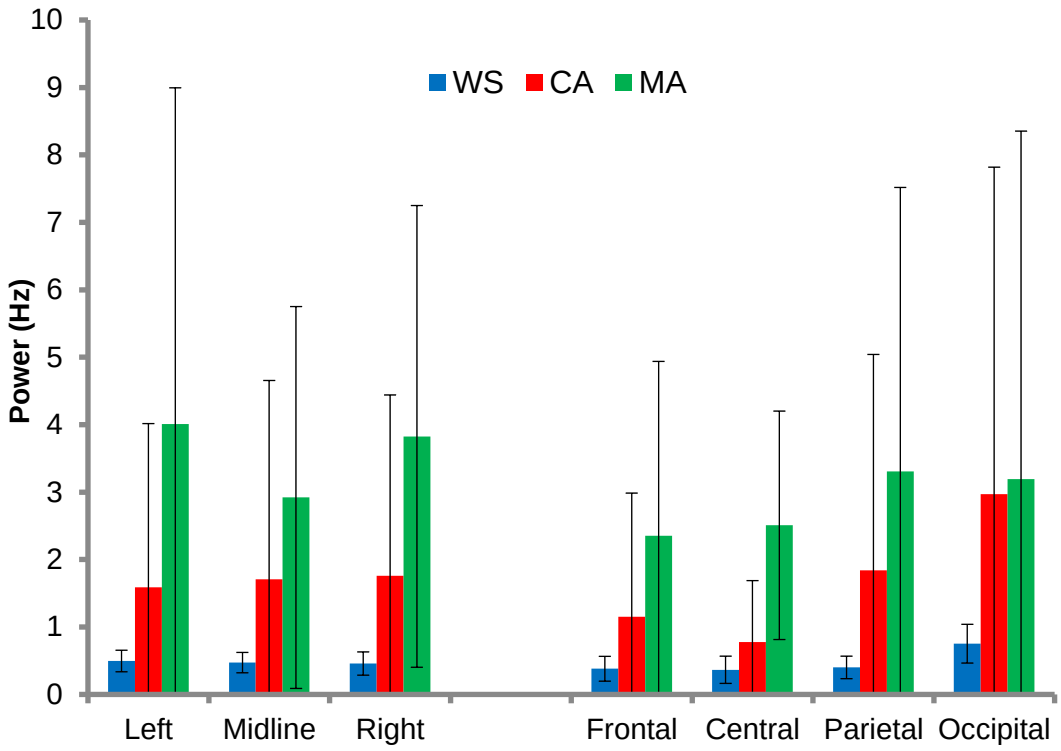


Figure 28: Mean absolute upper-alpha power (Hz) in the WS, CA, & MA groups by hemisphere and location in the Eyes Open condition. Error bars represent SDs

Group: Tukey post-hoc comparisons identified significantly greater *α-high* power in the MA group compared with the WS group (p=.027). There was no difference in *α-high* power between the WS / CA (p=.500) and the CA / MA (p=.208) groups.

Location: Pairwise comparisons identified a significantly greater occipital *α-high* power compared with the frontal (p=.001), central (p=.006), and parietal (p=.001) locations. Parietal *α-high* power was significantly greater than frontal (p=.015). There was no difference in *α-high* power between frontal / central (p=.682) and central / parietal (p=.133) locations.

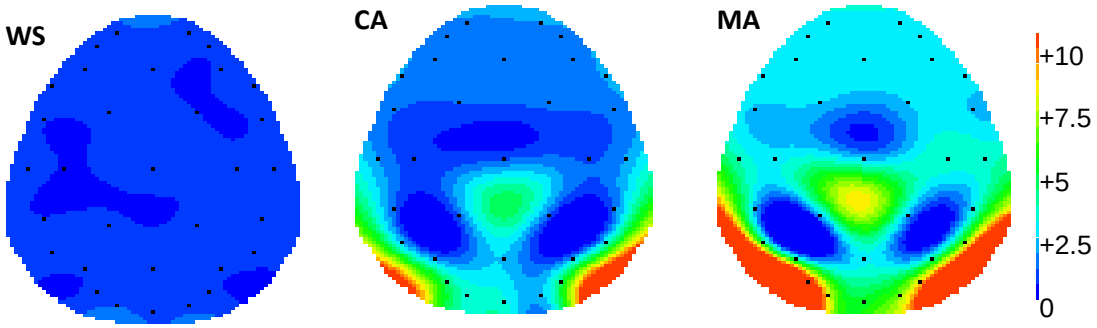


Figure 29: Spectral mapping of the upper-alpha band in the Eyes Open condition in the WS, CA, & MA groups

6.3.2.4 Beta band (β) – 13–29.5 Hz

The ANOVA indicated a significant main effect of location [F(2.119,65.694) = 13.523, p<.001], and main effects which approached significance for group [F(2,31) = 3.249, p=.052], and hemisphere [F(1.395,43.231) = 3.063, p=.074]. A significant interaction of group by location was also observed [F(4.238,65.694) = 3.091, p=.020]. All other interaction analyses were non-significant (p≥.267). See Figures 30 and 31.

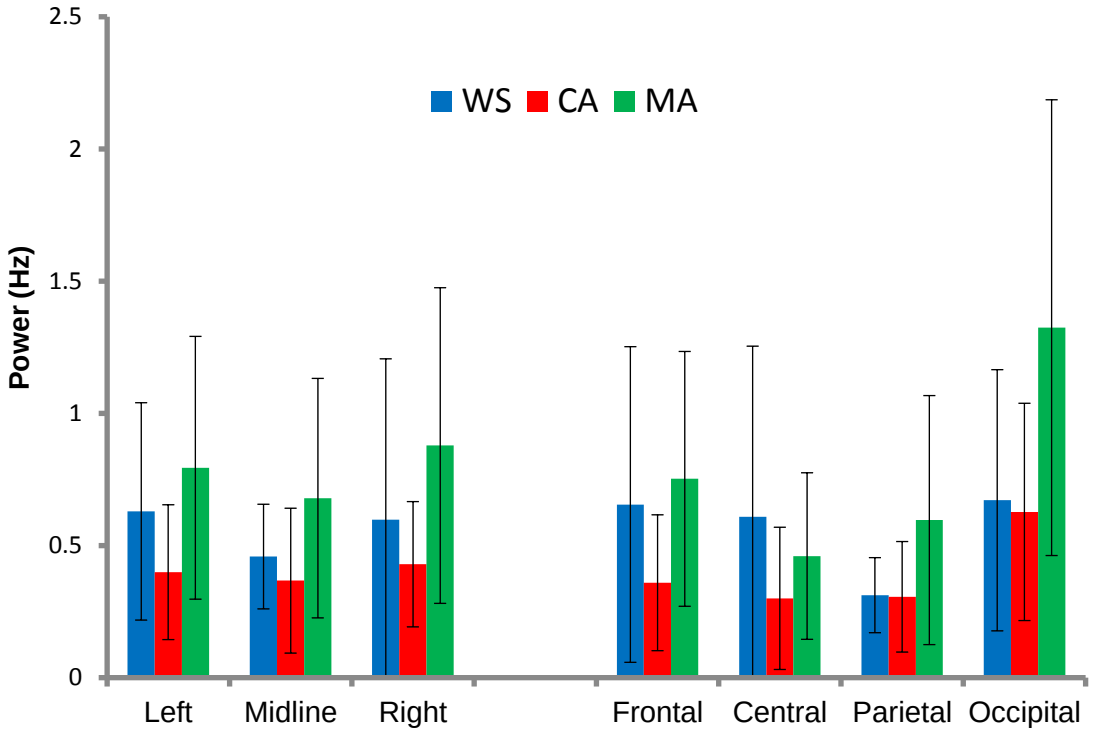


Figure 30: Mean absolute beta power (Hz) in the WS, CA, & MA groups by hemisphere and location in the Eyes Open condition. Error bars represent SDs

Group: Tukey post-hoc comparisons revealed significantly greater β power in the MA group compared to the CA group (p=.041), whereas non-significant differences were observed between the WS / CA (p=.516) and WS / MA (p=.346) groups.

Hemisphere: Pairwise comparisons revealed significantly attenuated β power at midline compared with both the left (p=.004) and right (p=.043) hemispheres. There was no difference in β power between the right and left hemispheres (p=.688).

Location: Pairwise comparisons revealed significantly greater occipital β power than observed frontally (p=.006), centrally, and parietally (both p<.001). In contrast, parietal β power was significantly attenuated compared with the frontal location (p=.007). The difference between frontal / central locations approached significance (p=.087) with greater β power observed frontally, but was non-significant between and central / parietal locations (p=.364).

*Location*group:* A one-way ANOVA identified significant differences by group in the parietal [F(2,31) = 3.313, p=.050], and occipital [F(2,31) = 4.529, p=.019] locations. Tukey post-hoc comparisons revealed significantly greater occipital β power in the MA group compared with both the WS (p=.046) and CA (p=.025) groups. The MA group also revealed numerically greater parietal β power, the difference approached significance compared with both the WS (p=.088) and CA groups (p=.067). All other analyses were non-significant (p≥.117).

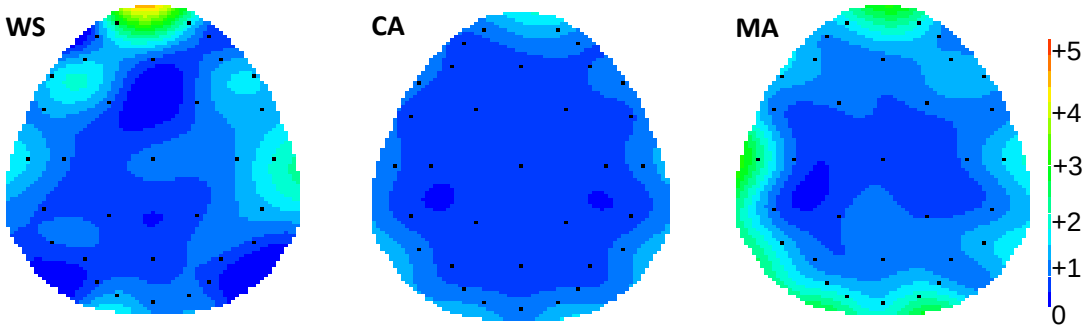


Figure 31: Spectral mapping of the beta band in the Eyes Open condition in the WS, CA, & MA groups

6.4 Discussion

The current study enabled us to move on from the previous chapters by examining the spectral profiles of the alpha and beta bands in adults with WS, and how these support the attentional and inhibitory deficits discussed throughout the thesis.The results of the current study are informative as, to date, there is no published research which evaluates the spectral power profiles of adults with WS during EC and EO resting states. Data analyses found that power in both the alpha (full and sub-bands) and beta bands observed in the WS group matched the topographical distributions observed in TD individuals during resting states. The analysis also confirms the WS group's profile is not reflective of their verbal mental age, therefore the discussion will focus primarily on the WS and CA group's results. The MA group's data will be addressed briefly at the end of this chapter and summed up in the General Discussion when considering control group matching in the thesis.

Overall, during the EC condition, all groups' EEG profile was characterised by a posterior topographical distribution as previously described (Barry et al., 2007; Chen et al., 2008; Klimesch et al., 2007). Full-alpha was accompanied with lateralised activity in the left and right sites compared with midline (Barry et al., 2007), whilst low-alpha showed a left hemisphere maximum. Upper-alpha was characterised by an occipito-parietal maximum as expected (Klimesch 1999; Klimesch et al., 2007) whist low-alpha band was characterised by a frontal-occipito-parietal distribution (Doppelmayr et al., 2002). Opening the eyes (EO) resulted in an overall attenuation of cortical activity in both alpha and beta bands

in all groups as expected in both typically developing individuals (Barry et al., 2007; Chen et al., 2008; Klimesch et al., 2007), and from the limited developmental disorder literature (ASD, Wang et al., 2013; ADHD, Woltering et al., 2012). Inspection of the full- and sub-bands of alpha identified the same topographical distributions by site as observed during EC. There were no differences in beta power by hemisphere on opening the eyes, however all groups' EEG profile was characterised by a fronto-occipital maximum (Barry et al., 2007; Chen et al., 2008; Mantini et al., 2007).

When considering results by group, overall, the differences were dominated by significantly greater alpha power in the MA group compared with the WS group during both the EC and EO conditions, and significantly greater beta in the MA group compared with the CA group during the EO condition, likely reflective of differences in oscillatory firing rates observed due to neuronal maturation (Uhlhass et al., 2010; Uhlhass & Singer, 2011). In contrast, the differences between the WS and CA groups were non-significant across all frequencies, though consistently numerically lower power in the full-alpha band and alpha sub-bands in both conditions was observed in the WS group. Interpretation of this needs to be addressed with caution due the lack of statistical significance that may be driven by small sample sizes. However, attenuated full- and low-alpha compared to the CA and MA groups was predicted based on the existing literature, with the numerically lower power consistent with other developmental disorders with attentional deficiencies including FXS (Van der Molen & Van der Molen, 2013), DS (Babiloni et al., 2009), and ADHD (van Dongen-Boomsma et al., 2010; Woltering et al., 2012). Therefore the current

study emphasises that such a pattern is not specific to WS, but is indicative of general developmental delay and therefore characteristic of any neurodevelopmental disorder (e.g. WS, FXS, DS, ADHD). In WS, significantly attenuated alpha power has been observed in research using combined EC / EO data (Ng et al., 2015), and in sleep states (Bódizs et al., 2014). In ADHD, attenuated alpha power during resting states is thought to reflect an ongoing state of cortical hyper-arousal even in the absence of cognitive processing (Loo et al., 2009); thus, the attenuated alpha power observed in the current study during both conditions could also be indicative of cortical hyper-arousal in WS. This is of notable interest due to the atypical behavioural attentional and inhibitory profile associated with WS (Davies et al., 1998; Little et al., 2013; Meyer-Lindenberg, Hariri et al., 2005; Porter et al., 2007) and warrants further investigation with greater sample sizes in order to establish whether these differences can be supported statistically.

In the beta band, there were no group differences between the WS and the CA controls during both conditions, which was not expected. Whilst previous research demonstrates greater beta power in WS during sleep (Bódizs et al., 2014), cortical and subcortical activity differs between resting- and sleep states (Cantero, Atienza, & Salas, 2002; Kaufmann et al., 2006; Larson-Prior et al., 2011). Thus the hypothesis of attenuated beta was guided by the ADHD literature, in which attenuated beta is widely documented as part of its EEG profile (e.g. Arns et al., 2012). Contradictory findings are also found in other developmental disorders; beta is attenuated in DS during EC (Babiloni et al., 2009), comparable to controls in FXS (Van der Molen & Van der Molen, 2013),

but inconsistent in ASD (Wang et al., 2013). Whilst these differences make interpretation of the functional significance of beta in developmental disorders more complicated, the comparable beta power between the WS and CA groups are informative here. Indeed, these comparisons across groups are hugely informative for the development of syndrome-specific theories. The beta band is typically associated with visuo-attentional processes (Gross et al., 2004; Kamiński et al., 2012; Seigel et al., 2012) and linked with motor control (Kilavik et al., 2013). It has been demonstrated in the thesis that behavioural performance (hit rates) in WS is comparable to controls during conditions of low attentional demands (e.g. Oddball, Chapter 5), but is impaired when attentional demands are great (SART, Chapter 4). Similarly, in Chapter 3, which adopted the LoP paradigm, the WS group performed better when provided with greater environmental support. [Of note, the emphasis here is on level of task difficulty, as greater RT in all of the aforementioned studies was indicative of general attentional deficits in this group of adults with WS.] Thus, the comparable levels in beta power between the WS groups and CA controls found here indicate that the small sample of individuals with WS recruited for this study (n=9) have a profile of resting-state cortical activation commensurate with successful attentional processing and motor control. Future research paradigms should therefore focus on beta power during resting states, and also during low- and high-attentional processing in a much larger sample of individuals with WS, in order to elucidate a) whether the pattern here can be replicated, b) at what stage in cognitive processing atypicalities (if any) in beta power manifest, and c) how these sub-serve their attentional deficits observed behaviourally. A further important area of research would be to investigate the alpha / beta ratio in WS,

and its impact during attentional processing (cf. Lansbergen et al., 2011). Currently, the dearth of research employing EEG methodology in WS makes interpretation of the current data more challenging.

The aforementioned questions may be in part answered by investigating the role of variability in the WS EEG profile. The issue of variability is widely documented in the WS, with high levels of variability typically associated with WS behavioural and cognitive phenotypes (Martens et al., 2008; Porter & Coltheart, 2005). Visual inspection of the current data noted an inverse pattern of variance, notably in the alpha band, with high variability in the control groups and low variability in the WS group. Thus, the lack of statistical significance between groups in the current study may be in part due to the high levels of variability identified in the alpha bands of the CA group. Low variability in the WS group was most evident in the upper-alpha band of both conditions, and low-alpha during EC; whereas the greater levels of variability in low-alpha during the EO condition were similar to that observed in the beta band. Though the functional significance is not clearly defined, low-alpha and beta are both associated with attentional processes (Kamiński et al., 2012; Klimesch et al., 2007; Seigel et al., 2012). A tentative interpretation of the results here is a dissociation in WS between the EO resting-state alpha oscillations which sub-serve general attentional processes and those with a greater functional association with more specialised cognitive processes. It must be emphasised again that this pattern of low variability is from a very small sample size and contradicts the heterogeneity typically associated with WS. However, this phenomenon of reduced variability has also been previously discussed in EEG research with ADHD adults (Woltering et al., 2012),

who also observed significantly less variability in the alpha band in adults with ADHD compared with healthy controls. Clearly this warrants much more research with large samples in order to elucidate whether the pattern found in the current study is reflective of the syndrome, or specific to these individuals with WS.

A final critique of the study relates to the mental age-matching procedure. The issue of appropriate control group matching has been commented on throughout the thesis, and specifically in *section 1.3.1* of the General Introduction. It was evident from the Oddball chapter and the current study that our group of adults with WS did not present the same ERP / EEG profile as children matched for verbal mental ability. As noted, numerically greater alpha and beta power was consistently observed the MA group compared with the WS and CA groups, in both the EC and EO conditions. In most analyses this was significantly greater than the WS group, but notably during the EO condition the MA group's beta power was significantly greater than the CA group. A caveat when comparing EEG profiles between adults and children is differences in oscillatory firing rates, as these are typically faster in children than in adults (for a discussion, see Uhlhaas & Singer, 2011); thus, frequency distributions between adults and children may not be comparable as the developmental profile of EEG oscillations is not complete until early adulthood (Uhlhass et al., 2010). The children in the MA sample here were aged from 8 to 16 years of age with the majority of participants aged ~12 years old, thus including verbal mental age-matched controls is not overly informative (see Sato et al., 2015, for an extensive study on developmental and child pathological comparison). Rather than mental-age matching, comparison with an atypically developing cohort such as ADHD would

be more beneficial in order to elucidate whether group differences are syndrome-specific, or due to atypical development in general. This will be addressed in greater detail in the General Discussion chapter.

In conclusion, to date the current study is the first known research project to evaluate the oscillatory profile of the alpha and beta bands in WS during EC and EO resting states. The overall profile provides a preliminary indication of the resting state EEG profiles which sub-serve the cognitive phenotype associated with WS. Whilst non-significant, the trend for numerically lower power in the alpha bands in WS compared to the controls is consistent with other developmental disorders characterised by attentional / inhibitory deficits such as ADHD, and may be indicative of a state of cortical hyper-arousal. In contrast, the comparable beta power between WS and CA groups during both EC / EO conditions suggests that their baseline EEG signature is commensurate with successful attentional processing, though this needs to be interpreted with caution due to the small sample size. Future research would benefit from focusing on beta power during active processing in order to elucidate differences in the beta profile in WS during low- and high-attentional conditions. Notably, the WS group's EEG signature also included a trend for low variability and this warrants further investigation with both larger sample sizes and a group of WS individuals with a more variable attentional profile. Future directions should also focus on functional connectivity and include fMRI methodology. Issues relating to mental-age matching have been addressed. Finally, the small number of participants in all groups may impact on the results, thus all future research would benefit from recruiting a larger sample in order to verify the findings from the current study.

Chapter 7: General Discussion

7.1 Summary of the main findings

The aim of the thesis was to examine cognitive and executive functioning in older adults (aged 35+yrs) with WS, as to date the available literature which focuses on this cohort is notably limited. The principal objective of Chapter 2 was to investigate AM performance in adults with WS aged 35+yrs, and examine whether deficits could be attributed to premature cognitive ageing in the syndrome. The results found no evidence for premature cognitive ageing; rather, they supported the existing literature that identifies 'binding' as problematic in adults with WS (Deruelle et al., 2006; Jarrold, Phillips, & Baddeley, 2007; Vicari et al., 2005). Specifically, the results indicated an inability in the WS group to show a 'typical' ability to capitalise on semantic memory during both item- and paired-associates recognition, and an inability to implement 'typical' spontaneous encoding strategies in the absence of a semantic relationship between the paired stimuli. Chapter 3 moved on from this and aimed to elucidate whether a LoP paradigm could provide a supportive role to the deficient semantic memory and spontaneous semantic encoding strategies described in Chapter 2. The results found all groups, irrespective of the presence / absence of WS, benefited from deeper encoding of study items as predicted. All groups demonstrated significantly greater recall of deeply encoded items compared to those encoded with shallow processing, though with greater variability and latency by the WS group. Notably, in both Chapters 2 and 3, the WS group had greater FA rates and

RT to errors, indicative of deficiencies in error monitoring and re-engagement of attentional processes. Thus, the data from Chapters 2 and 3 highlighted the importance of exploring the area of EF within the cognitive profile, since the successful engagement of such processing mechanisms is closely related to everyday cognitive ability.

Chapter 4 employed the SART to measure response inhibition and lapses of attention, as these are executive skills with clear implications for understanding wider deficits related to facets of the WS phenotype. The WS group presented overall atypicalities in sustained attention and inhibition, evidenced by lower hit and greater FA rates compared to CA controls, but not TD older adults aged 65+yrs. Also there was no difference in WS group's RT pre- and post-error, thus demonstrating they were unable to re-establish executive control of behaviour to maintain sustained attention performance, similar to that observed with individuals with traumatic brain injury (TBI). In contrast, both the CA and 65s groups' RT increased post-error, indicative of successful error monitoring and the re-establishment of controlled processing during sustained attention.

Building on from the results of the behavioural paradigms in Chapters 2, 3, and 4, the electrophysiological section of the thesis emphasised the need for converging evidence from neuroimaging methodologies in developmental disorder research (Grice et al., 2001; Haas et al., 2009, 2013; Key & Dykens, 2015). This section adopted ERP and EEG methodologies in order to explore atypicalities in the neural mechanisms sub-serving attentional and inhibitory deficits described in Chapter 4, and which can be attributed to the episodic and

semantic memory deficits observed in Chapters 2 and 3. Chapter 5 adopted ERP techniques and the three-stimulus Oddball task, as this task is sensitive to the neural mechanisms of attention and inhibition (Donchin et al., 1978). The results found attenuated N2 amplitude in response to both the novel and target stimuli in WS, indicative of impaired attention. Comparable P3a and P3b amplitudes demonstrated successful orienting response to rare stimuli, and the comparable P3b latency indicated appropriate WM updating in WS compared with CA controls. In contrast, the significantly longer P3a latency indicated impairments in the mechanisms required to disengage from task-irrelevant stimuli and redirect attention to task-relevant stimuli. The final empirical chapter (Chapter 6) adopted EEG methodology to investigate baseline cortical activity during resting states which may also sub-serve the attentional and inhibitory behavioural profile described in the previous empirical chapters. Whilst non-significant, the results found a trend for numerically lower power in the alpha bands in WS compared to CA and MA controls. This is consistent with other developmental disorders characterised by attentional / inhibitory deficits such as ADHD, and may be indicative of a state of cortical hyper-arousal (Loo et al., 2009). In contrast, the comparable beta power between WS and CA groups during both the EC / EO conditions suggests that their baseline EEG signature is commensurate with successful attentional processing.

Notably, the inclusion of a control group of TD children in Chapters 2, 5, and 6 has demonstrated that both the behavioural and electrophysiological profiles observed in the adults with WS in the paradigms adopted here were not reflective of delayed development. This indicates that the cognitive and executive

processes under investigation have developed with increasing age, thus this group of adults with WS presented behavioural and electrophysiological profiles reflective of their intellectual difficulties. However, caution needs to be addressed where effects were marginal and did not reach statistical significance, most likely reflective of overall small sample sizes. Here we can only infer a trend in the data, and further analyses such as effect sizes, confidence intervals and multiple comparisons (e.g. Bonferroni / Tukey LSD corrections) may be informative in interpretation of the results (e.g. Chapter 3). Future experimental work is desirable in order to confirm these marginal effects.

7.2 Associative memory profile in older adults with WS

The General Introduction discussed that, whilst WS has received a wealth of interest in the developmental disorder research, to date the research focusing on older adults with WS is limited (e.g. Devenny et al., 2004; Howlin et al., 2010; Krinsky-McHale et al., 2005; Porter & Dodd, 2011). Thus, unlike our understanding of changes in cognition in individuals who are ageing typically, our knowledge of how changes in cognitive processes manifest in older adulthood in adults with WS is notably lacking. Primarily, an AM paradigm was adopted to investigate claims of premature cognitive ageing adults with WS (aged 35yrs+). Overall impaired AM performance in WS did not support these claims, rather a consistent deficit accessing semantic memory was observed in both visual and verbal domains. AM is a type of episodic memory and which requires the retrieval of contextual information from episodic LTM (Chalfonte & Johnson, 1996; Naveh-Benjamin et al., 2003). In WS, verbal and visuo-spatial LTM are relatively impaired (Brock, Brown, & Boucher, 2006; Sampaio et al., 2008), whereas visuo-

object LTM is relatively preserved (Vicari et al., 2005). The deficits accessing semantic memory observed in the WS group in the verbal paired-associates task may be indicative of an atypical relationship between episodic and semantic memory, due to poor overall LTM abilities and over-estimated lexical-semantic knowledge previously documented in this group (Purser et al., 2011; Vicari et al., 2000). The deficits in both the verbal and visual tasks have also been identified in other developmental disorders. In ASD, impairments in retrieval of information from LTM are observed when the to-be-remembered items are semantically or contextually related (Tager-Flusberg, 1991), whilst impaired relational memory is found in ASD when spontaneous encoding is required (Gaigg, Gardiner, & Bowler, 2008). Furthermore, a recent meta-analysis (Skodzik, Holling, & Pedersen, 2013) noted domain differences, with significantly impaired verbal LTM, but spared visual LTM in adults with ADHD compared to healthy controls. Thus, these LTM deficits may not be restricted to WS (e.g. may not be syndrome-specific) and indeed may be indicative of any form of intellectual difficulty, and future research would benefit from taking a cross-syndrome perspective (with comparison groups such as ASD, ADHD, and FXS) to investigate the specificity of domain differences and semantic deficits.

Importantly, impairments in AM performance observed in the WS group in Chapter 2 were more likely reflective of deficiencies during encoding rather than at retrieval. This is of note as the paradigm adopted in the visual paired-associates task in Chapter 2 provided no support during encoding, due to the lack of a semantic relationship between the paired stimuli. Similarly, in the verbal paired-associates task, whilst the semantically related condition contained 10

semantic groups, no category cues were provided during either encoding or retrieval. The only other known behavioural study investigating AM performance in WS encouraged a deeper level of encoding ('Yes / No' pleasantness judgement) and greater environmental support at retrieval (target stimulus plus two foils) for both item- and associative-recognition (Costanzo et al., 2013). However, this only benefited item-recognition performance, whereas AM performance was significantly impaired compared to controls. The only two published studies (Devenney et al., 2004; Krinskey-McHale et al., 2005) which to date have found evidence of premature cognitive ageing in adults with WS, also encouraged deeper encoding by providing semantic categories for each stimulus during the encoding phase. At retrieval, participants initially performed free recall thus received no environmental support. For any un-remembered items, participants were provided with the category cues to assist recall. However, irrespective of semantic category cueing and greater environmental support, performance was still impaired in the WS group compared to the comparison group with intellectual difficulties (Devenney et al., 2004; Krinskey-McHale et al., 2005). These differences may therefore reflect differences between subjective and objective judgements, whereby a 'Yes / No' pleasantness response enhances the memory trace to a deeper level. Thus, it is possible that the instructions at encoding are more pertinent than the level of environmental support at retrieval. However, due to the dearth of information in the developmental disorders literature, future research should focus on different levels of encoding in order to elucidate how these support episodic memory in WS, especially in comparison to other disorder groups and typical development, and contribute to our theoretical understanding.

An alternative explanation for the AM profile observed may relate to impaired EF. The conscious retrieval of bound information places great demands on attentional resources (Liftshitz et al., 2011; Vicari et al., 2000). In typical development, greater FA rates can be indicative of atypical attentional processing, especially in the ageing population (Staub, Doignon-Camus, Després, & Bonnefond, 2013), whilst inhibitory deficits are associated with atypical semantic processing, likely due to impaired inhibition of contextually irrelevant information (Hoenig & Scheef, 2009). As outlined in the General Introduction (*section 1.1.9*), research has identified a wide range of deficits of EF in WS; pertinent to Chapter 2 are atypicalities in inhibitory (Atkinson et al., 2003; Menghini et al., 2010; Mobbs, Eckert, & Mills et al., 2007; Porter et al., 2007), and attentional processes (Atkinson & Braddick, 2010 Menghini et al., 2010), though there are discrepancies in the literature also with regard to modalities affected (see Costanzo, Varuzza et al., 2013). The WS group's performance was characterised by large FA rates in the verbal paired-associates task, and both the visual item recognition and paired-associates tasks, which may be due to attentional / inhibitory dysfunction. However, regarding the visual paired-associates task, the WS group's FA rate was comparable with the 65s group, therefore interpretation of this result is more difficult, especially due to the dearth of literature investigating AM in WS. In the discussion of Chapter 2, three possible suggestions were made to explain this finding: a) both groups were unable to form spontaneous encoding strategies in the absence of a semantic manipulation; b) both may have responded to the familiarity of the individual items in the pairing rather than to the association between the items; and c) the

replaced picture in each rearranged pair was too similar to the original, thus both the WS and the 65s participants were unable to detect the change. This latter suggestion seems more likely as the CA group's FA rate was at chance level which also indicates greater difficulty correctly rejecting previously unseen items.

However, a recent study which has used neuroimaging techniques to investigate familiarity / recognition processes in WS has provided a preliminary indication of atypicalities in frontal activity that may help interpretation. Employing ERP methodology, Key and Dykens (2015) investigated the neural mechanisms sub-serving the heightened sociality traits in adults with WS (mean age 26yrs, SD 8.29), and compared this with an age-matched typically developing control group (mean 26.9yrs, SD 8.82). Their paradigm included social (faces) and non-social (houses) stimuli. Participants were exposed to familiar (repeated) and unfamiliar (unrepeated) stimuli but given no encoding instructions; rather they made a behavioural response to a non-target stimulus. The repeated face stimuli were expected to be more salient in the WS group due to their hypersocial and pro-social drive (e.g. Jones et al., 2000; Riby & Hancock, 2008), and thus produce a stronger parietal recollection ERP response; however this effect was only observed in the typical control group. Furthermore, the WS group showed no discrimination in their frontal old / new ERP response between the houses and faces stimuli, whereas greater frontal response to the houses was observed in the TD controls. Thus, despite the behavioural propensity for heightened social interest in WS, their electrophysiological signature did not support this. Of note, the paradigm did not include paired-associates; thus is only informative here with regard to item recognition. Clearly this is under-researched in the literature and

needs to be investigated incorporating AM paradigms; however, this study provides a first indication of how the neural correlates of familiarity / recollection differ in WS.

It must be noted that the paradigm adopted for Chapter 2 was based on previous research with TD individuals (Naveh-Benjamin et al., 2003); however it may not have been appropriate methodology to incorporate in research with a population with a developmental disorder. Furthermore, methodological inconsistencies in the design of the study prevent cross-domain comparisons. At the time of testing there was no comparable research published which investigated AM abilities in individuals with WS; thus the rationale of Chapter 2 was to replicate methodology undertaken with TD older adults. The design of the verbal item-recognition and paired-associates tasks required participants to read, encode, and identify a semantic relationship between a word pair within a relatively short temporal window. Whilst previous literature demonstrates that this is suitable methodology to use with TD individuals, the design of the verbal task may have been too demanding for the WS group. Only fifteen of the WS group were able to comply with the task demands in the verbal tasks, whereas all participants were able to complete the visual task. Verbal ability is relatively less impaired in WS; however the results of Chapter 2 support the work by Krinsky-McHale et al. (2005) who also observed impaired verbal LTM during a demanding episodic task. In the visual paired-associates task, the pattern of data suggests that the WS group may have responded to the familiarity of the individual images in each pair, rather than the association between them. Certainly this has been highlighted previously as a caveat when considering the methodology employed

in AM research with individuals with WS (Costanzo et al., 2013). In their study, the participants had to distinguish between a target and foils in both the item- and paired-associates tasks. In the item-recognition task the target was among eight foils. Therefore the response required the participants to identify the correct target through a familiarity judgement (their performance approached ceiling level) rather than making a 'Yes / No' response, as was the case in Chapter 2 and which could result in chance performance. For the associative recognition, the participants had to identify the second image in the pairing from a choice of three similar images (all were included in the study phase). As all three images would be familiar to the participant, identification of the association would require the correct recollection of the second picture in the pair. Their methodology provides a more robust measure of recollection compared with Chapter 2. Future research should replicate this paradigm with an older cohort of adults with WS in order to clarify whether the differences between the results in Chapter 2 and Costanzo et al. (2013) are due to the differences in the design of the tasks or reflect changes with increasing age.

7.3 Semantic support during encoding on episodic memory performance

In light of the inability to capitalise from semantic memory and implement spontaneous semantic encoding strategies observed in Chapter 2, the LoP paradigm adopted in Chapter 3 (Craik & Lockhart, 1972) was ideally suited to examine how both episodic and semantic memory interact to support memory performance in adults with WS. From interpretation of the data in Chapter 3, it was posited that these adults with WS presented a LoP profile that did not reflect either their chronological or mental age. The CA group's performance

approached ceiling level in the deep encoding condition, and was significantly greater than both the WS and MA groups. Thus, the CA controls' performance supported the widely documented LoP bias and the ability to also implement a spontaneous semantic encoding strategy as noted in the literature (Craik & Lockhart, 1972; Luo et al., 2007). Successfully remembering previously studied items was relatively impaired in WS compared to the CA-matched participants, but not the MA group. It could be claimed that this group did show a deficit of episodic memory in general, but that deficit was entwined with their general level of intellectual functioning, here shown by their verbal mental age. In contrast, whilst the overall statistically comparable performance between the WS and MA groups suggests WS performance was reflective of their mental age, these similarities may reflect different processing mechanisms in WS, specific to the syndrome (cf. Hsu, Karmiloff-Smith, Tzeng, Chin, & Wang, 2007). Indeed to support this suggestion, the numerically lower hit rates and increased RT during the recognition of previously studied items provide the tentative suggestion that individuals with WS may have less efficient and atypical search processes through LTM compared to both CA and MA individuals.

It should be noted that the reduced advantage of deep versus shallow encoding in the WS group is in line with the research highlighted previously in the thesis, outlining the recollection versus familiarity distinction during episodic memory retrieval in WS (Costanzo et al., 2013). Although WS participants benefited from a semantic support strategy at encoding, the finding of equivalent performance in the shallow, and a deficit in the deep, encoding condition compared to the control groups was also indicative of a recollection deficit.

Further work is clearly required examining in more detail the semantic strategies employed by individuals with WS during an episodic memory task, and also the retrieval mechanisms that are engaged as a result of these strategies. The emerging evidence from the ERP literature already highlighted in the thesis may help elucidate the neural signature that supports strategy differences (e.g. recollection versus familiarity; Key & Dykens, 2015), and thus guide the direction of future research.

Highly pertinent to the thesis was the inspection of the controlled processing and monitoring mechanisms involved in episodic memory (e.g. Gallo, 2004; Johnson, 2006). Post-retrieval monitoring processes (correct rejections and FA rates to new unstudied items as a marker of impaired memory processes) are engaged during uncertainty when making a judgement regarding the status of a test item. The significantly larger FA error rates made by the WS group when rejecting new items was accompanied by an increased RT when correctly rejecting new items, thus is reflective of the executive dysfunction associated with the syndrome (Rhodes et al., 2010). Being more disposed to false memories suggests that the recognition paradigm employed here did not produce a situation where the new items were distinctive enough for the WS group to reject them as an unstudied item. An increase in both errors and RT for correct rejections in the WS group suggests uncertainty or poor decision-making ability when identifying an unstudied item. Furthermore, even after more consideration and monitoring of responses, the WS group had more false memories. This provides further evidence that poor error monitoring may be a key characteristic of the WS profile (e.g. Smith, Gilchrist et al., 2009).

Whilst executive dysfunction in WS can explain group differences observed in the deep condition, all three groups presented a comparable level of ability in the shallow condition. The aim of the shallow encoding question ('*Is the next item in a frame?*') was to focus on the perceptual features of the item. However, the presence of the frame may have directed the participants' focus to the perceptual components of the overall array, thus drawing attention away from encoding the to-be-remembered stimuli. This was evidenced by the high levels of variability observed in both the CA and the MA groups, despite no difference between all three groupsin hit rates irrespective of whether the frame was present or not during encoding. However when applying a LoP perspective to the WS data, it is important to acknowledge the widely documented bias for perceptual processing associated with the visuo-perceptual profile of the WS phenotype (Farran et al., 2003). Typically, individuals with WS show a bias towards processing local features rather than global features (Rondan, Santos, Mancini, Livet, & Deruelle, 2008), but can also perceptually discriminate between global and local features (Porter & Coltheart, 2005). The pattern of data from Chapter 3 suggests that the WS participants were able to discriminate between the presence of the frame (global) and the to-be-remembered item (local). Thus, they did were not susceptible to the same interference at encoding as found in the control groups, and their high level of variability was consistent with the heterogeneous WS profile (Porter & Coltheart, 2005).

7.4 The role of executive functioning in episodic and semantic memory in WS

The thesis has highlighted how the deficits in episodic and semantic memory ability observed in the WS adults in both Chapters 2 and 3 are likely due to atypicalities in EF. Of note, successful semantic processing requires the inhibition of irrelevant information (Debruille, 2007). Inhibition has been studied with regards to cognitive (Costanzo, Varuzza et al., 2013) and social functioning (Little et al., 2013); however neither of these research paradigms have provided a comprehensive comparison of different metrics of attentional lapse and inhibition in an older WS group, and when completing a task known to be related to everyday cognitive failures (Smilek et al., 2010). The findings from Chapter 4 demonstrated that the SART paradigm was a sensitive measure for examining different aspects of attentional lapse and inhibition in WS (also see Seli, 2016, for a critique of the SART as a sensitive measure of attentional lapse cf. motor decoupling).

The primary finding from Chapter 4 was an inability in the WS group to re-establish controlled error monitoring processes during sustained attention, evident from the failure to decelerate RT following a FA commission error, and which is observed in other populations with known frontal lobe and associated executively controlled processing deficits such as TBI (Robertson et al., 1997). Post-error slowing after a FA commission error is an important indicator of error monitoring and the re-establishment of controlled processing during sustained attention. In typically ageing adults, this aspect of EF is relatively well preserved during continuous performance tasks like the SART (e.g. McVay et al., 2013); however, with more severe frontal lobe deficits the pattern is somewhat different.

As noted in the thesis, individuals who have suffered from TBI, characterised by frontal lobe and white matter damage, fail to decelerate their behavioural response after an error on the SART (Dockree et al., 2004; Robertson et al., 1997). The WS group in Chapter 4 presented this exact pattern, and, whilst caveats have been raised with regard to the sample size, this finding is notable evidence for a failure in re-establishing executive control of behaviour to maintain sustained attention. This has also been found in other domains; Smith, Gilchrist et al. (2009) also observed impaired error monitoring in spatial cognition, where inefficient visual search performance was characterised by a lack of monitoring of previously visited spatial locations. Therefore, rather than showing parallels to a typical ageing profile, the WS adults displayed inhibitory processing deficits consistent with those who have received TBI (Robertson et al., 1997). Elsewhere, in the WM domain, lower hit rates accompanied by higher FAs were observed in a TBI population, further supporting similarities between WS and TBI profiles (Slovarp, Azuma, & LaPointe, 2012). However, see Thomas and Karmiloff-Smith (2002) for a critique on the comparison of individuals with developmental disorders with those who have acquired brain injury.

Considering the claims of premature cognitive ageing in WS as outlined in the General Introduction (*section 1.1.4*), inspection of the pattern between the CA and the 65s groups in Chapter 4 was informative. The results indicated that the older TD adults (65s group) were making speed–accuracy trade-offs, due to the numerically (but not statistically significant) lower FA rates / greater RTs compared with the CA group (also found in Chapter 2). However, as this pattern was not evident in the WS group, the results of Chapter 4 further question the

claims of premature cognitive ageing in WS (cf. Krinskey-McHale et al., 2005). As the results are more indicative of inhibition deficits, comparison with the ADHD literature also aids interpretation (Sergeant, 2000, 2005). A meta-analysis by Geburek and colleagues (2013) found that, despite heterogeneity across the individual studies, adults with ADHD also made more FA errors of commission on *Go / No-Go* tasks, but showed no differences in RT compared to TD controls. The authors interpret this as reflective of the impulsivity central to ADHD; their propensity to respond prevented inhibitory processes, resulting in decreased RT and therefore failure to control erroneous motor action. It was critiqued in the meta-analysis that there was high variability between studies in RT, and not indicative of a consistent trend for slower RT in ADHD during correct withholds, which may be in part due to different task paradigms. However, in Chapter 4 the analysis of variability in RT data during the duration of the task was informative, further indicating how WS participants were unable to exert controlled processes to maintain focus during the task. Inspection of variability in RT has been useful in previously both assessing cognitive markers and as a strong predictor of impairment of ADHD (Williams et al., 2010), emphasising further the similarities of the cognitive difficulties observed between WS and ADHD (but also see Coghill et al., 2014).

7.5 ERP signature underlying the attentional and inhibitory profile in WS

In order to complement the results from the behavioural section of the thesis, the electrophysiological section investigated the neurocognitive mechanisms sub-serving the attentional and inhibitory deficits in adults with WS. Chapter 5 investigated the pattern of ERPs engaged during a three-stimulus

Oddball task. Overall, the results indicated atypicalities in earlier and later ERP components, and a dissociation between involuntary and voluntary attentional processing, and WM updating. The main findings were as follows: despite 100% accuracy responding to the target stimulus in all groups, compared to the CA group, the WS group's ERP profile was characterised by attenuated N2 peak amplitude in response to the novel and target stimuli, an increase in P3a peak latency in response to the novel stimulus, and no P3b peak amplitude or N2 / P3b peak latency differences in response to the target stimulus. Compared to both TD control groups, the results are indicative of atypical neural mechanism in WS when orienting to a rare stimulus (novel and target N2), and a temporal delay in the disengagement from a rare task-irrelevant stimulus (P3a).

One theoretical perspective posits that the N2 component in *Go* / *No-Go* paradigms reflects conflict arising from competition between the execution (target) and the inhibition (novel) of a single response (Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003). A larger N2 is typically observed frontally and / or centrally when an overt response needs to be withheld, thus motivated by inhibition of a planned response (Bruin & Wijers, 2002) whereas a reduced novel N2 is indicative of an ongoing propensity to respond (Folstein & Van Petten, 2008). This approach is highly pertinent as the numerically greater N2 amplitude at FZ (CA group) and CZ (MA group) in response to the novel stimulus indicated appropriate neural responsivity required for successful inhibition in both TD control groups. In contrast, the overall attenuated N2 amplitudes observed in the WS group, especially in response to the novel stimulus, demonstrated deficiencies in earlier components that regulate conflict monitoring processes

during *Go / No-Go* discrimination. As inspection of the literature identifies greater novel N2 negativity in other developmental disorders during Oddball paradigms (e.g. Fragile X syndrome, Cornish et al., 2004; Rett syndrome, Stauder, Smeets, van Mil, & Curfs, 2006), these conflict monitoring deficits likely manifest as an erroneous syndrome-specific default mode in WS resulting in a continuing propensity to respond.

In typical development, larger N2 amplitudes are associated with fewer errors of commission on *No-Go* tasks, indicative of an association between amplitude and successful conflict monitoring / response inhibition (Falkenstein, Hoormann, & Hohnsbein, 1999), whilst attenuated N2 / P3 peak amplitudes are observed during erroneous behavioural responses (O'Connell et al., 2009). Neuroimaging research has sourced successful / unsuccessful N2 conflict monitoring during *Go* / *No-Go* methodologies with activity in the anterior cingulate cortex (ACC; Luus, Van Snellenberg, & Liotti, 2007; Mathalon, Whitfield, & Ford, 2003). The ACC contributes to early preparatory and orienting mechanisms, and subsequently engages cognitive control via the dorsolateral pre-frontal cortex (DLPFC) in order to resolve the conflict (Carter & Van Veen, 2007). Despite underactive ACC and DLPFC in WS during response inhibition (Mobbs, Eckert, Mills et al., 2007), comparable behavioural performance with TD controls found in Chapter 5, and by Mobbs, Eckert, Mills et al. (2007), suggests that this group are able to implement cognitive strategies to overcome these processing deficits.

Whilst the WS group's behavioural RT was significantly longer compared to the CA group, accuracy performance in all groups reached ceiling level.

Contrast this with the results from the SART (Chapter 4) where accuracy was at chance level. One possibility is that they were able to overcome attentional deficits due to the low task demands, with the increase in behavioural RT reflecting a speed–accuracy trade-off as previously described (Mobbs, Eckert, Mills et al., 2007). It has already been demonstrated in the behavioural section of the thesis that level of task difficulty affects task performance in WS disproportionally compared to the TD controls (e.g. AM / SART cf. Oddball). Thus, it can be inferred that, under conditions which do not over-stretch the attentional abilities of these individuals, these adults with WS were able to engage the cognitive control required for successful task performance. This was highlighted in the study by Key and Dyckens (2011), who demonstrated an atypical neural profile only in response to local stimuli rather than global stimuli, despite a preference for local processing being a known trait in the WS behavioural profile (Rondan et al., 2008). This juxtaposition highlights the need to also focus on the neural response during more effortful processing, and where lapses in attentional processing are evidenced by errors of commission (false alarms). After an error of commission, ERP negativity 50–100ms post-response is observed in TD individuals, known as error-related negativity (ERN), indicating an awareness at the neural level of an erroneous response (Yeung, Botvinick, & Cohen, 2004). This is accompanied by a tendency to increase behavioural RT immediately following an error (Smallwood et al., 2006). The thesis has identified at the behavioural level (SART; Chapter 4) that adults with WS have deficient error monitoring ability, evidenced by a speeding up of behavioural RT post-error of commission. It was not possible to analyse the ERN in the current study as visual inspection of the data identified only a limited number of errors in all three groups

and did not generate enough ERP trials that could be analysed statistically. Thus, to provide a more comprehensive understanding of the neural substrates of attentional / inhibitory deficits in WS, future paradigms would benefit from adopting more challenging tasks likely to result in errors of commission, to enable analysis of the ERP profiles of both correct and erroneous response patterns.

To the best of our knowledge the Oddball methodology adopted in Chapter 5 has not been used to date in research with individuals with WS; thus the results have provided previously undocumented evidence of the neural profile of involuntary and voluntary attentional processes in the syndrome. However, there are certain methodological issues to consider with the Oddball paradigm. Both the N2 and P3a habituate on repeated exposure to the same stimulus, and this habituation continues into second and ongoing blocks of presentation (Courchesne, Hillyard, & Galambos, 1975). Furthermore, the N2 is not influenced by task difficulty; rather it is sensitive to perceptual deviation from the other stimuli (Polich & Comerchero, 2003). Thus, it is possible that the comparable P3a peak amplitude profile observed in the WS and the CA groups reflects habituation processes, whilst the attenuated novel and target N2 peak amplitudes in the WS group are indicative of neuronal dysfunction in perceptually discriminating between the novel and target stimuli from the frequent stimulus, despite object perception being a robust trait (Landau, Hoffman, & Kurtz, 2006). Future research adopting an Oddball paradigm would benefit from including unrepeated novel stimuli as this would provide a purer P3a response, and more distinct differences between the frequent and target stimuli in order to eradicate these possible

confounds (see Polich, 2007, for discussion of task parameter manipulations within the Oddball task).

7.6 EEG profile of resting states

The final empirical chapter of the thesis evaluated the spectral power profiles of the alpha and beta bands in adults with WS during both EC and EO resting states. The results found that power in both the alpha (full and sub-bands) and beta bands observed in the WS group matched the topographical distributions found in TD individuals during resting states. Alpha power (full and sub-bands) was attenuated compared to the CA controls in both conditions. Though none of the analyses reached significance, this pattern was consistent with other developmental disorders with attentional deficiencies, possibly due to a chronic state cortical hyper-arousal rather than being a syndrome-specific characteristic of WS. In contrast, the comparable beta power between the WS and the CA groups provides a preliminary indication of a resting state EEG profile in WS commensurate with successful attentional processing, but this can only be applied to the current sample of adults with WS. Therefore, whilst the sample in Chapter 6 was small, considering the functional significance of beta with motor control and attentional processing, the results from Chapter 6 are noteworthy, though must be addressed with caution.

Secondly of note, is the difference in variability between the frequency bands in the EEG profile of the WS group. WS is typically associated with large heterogeneity both cognitively and behaviourally, however the inverse pattern of variance, most notably the upper-alpha band, suggests the lack of statistical

significance between groups in the current study was due to the high levels of variability in the CA group's data. Visual inspection of the variability in the ERP data from the Oddball task (Chapter 5) from the WS group did not identify an unusually low pattern compared to the CA group as found in the EC / EO study. However, the similarities in the profile of resting states alpha band variability documented in the WS group and with ADHD adults (Woltering et al., 2012) further highlight the importance of investigating the variability profile in developmental disorders from neurophysiological research endeavours, in order to link these with behavioural and cognitive processes. This is emphasised by emerging theoretical perspectives which posit that low variability in oscillatory brain states is indicative of greater behavioural variability, suggesting that atypical oscillatory firing is a neural marker in developmental disorders (Klein, Wendling, Huettner, Ruder, & Peper, 2006; McIntosh, Kovacevic, & Itier, 2008). For example, TD individuals who have suffered a TBI present similar attenuated EEG power to that observed in developmental disorders, but also high variability in their EEG profile as is observed in non-brain damaged healthy individuals (Roche et al., 2004). Evidence for this dissociation can be found when comparing behavioural and neuroimaging data. A recent behavioural study found high levels of variability, which were accounted for when chronological age was applied to the analysis as a covariate (Van Herwegen, Rundblad, Davelaar, & Annaz, 2011). This negated the variability between children with WS (n=33) and typically developing CA-matched controls on standardised measures of verbal mental ability, and reduced variability on a visuo-spatial task. In contrast, Ng, Brown et al. (2015) applied chronological age as a covariate to data from an fMRI paradigm with WS adults (n=20) but this did not account for the variability in their BOLD

data. Similar covariate analyses applied to the data from Chapter 6 also found no effect of chronological age on the variance in both alpha and beta power (thus not presented). It cannot be discounted that the differences between Van Herwegen et al. (2011), Ng, Brown et al. (2015), and the current study are due to developmental maturation as the participants in both the current study and Ng, Brown et al. (2015) were adults. Alternatively, it may reflect the smaller sample size recruited in both Ng, Brown et al. (2015) and the current study (n=9), whereas the sample recruited by Van Herwegen et al. (2011) was notably larger. Despite issues regarding sample size, this demonstrates the importance of variability in neuroimaging as well as behavioural data, which thus far is under-researched in developmental disorders. Notably, within syndrome variability is a 'hot topic' in the current developmental disorders literature (e.g. Charman, 2015).

It was highlighted in the General Introduction and in Chapter 6 that the EC and EO conditions represent two functionally distinct processes of the attentional system; EC is thought to represent the baseline state of cortical arousal, and EO reflects a baseline measure of cortical activity in preparation of task activity (Barry et al., 2007). Previous authors have commented that inconsistencies between research findings may be due to methodological differences (EC cf. EO; Bresnahan & Barry, 2002; Clarke et al., 2008) as well as the oscillatory power examined (absolute cf. relative power; Bresnahan, Barry, Clarke, & Johnstone, 2006; Koehler et al., 2009). Of note, the only known study published to date that focuses on resting states in WS (Ng et al., 2015) combined the data from the EC and EO conditions; therefore it is not possible to dichotomise how the profile between EC and EO resting states in WS differs from controls. The literature

emphasises the EC condition as a resting state in the absence of sensory processing. Whilst this is accurate with regard to visual stimulation, research paradigms rarely control for the exclusion of auditory sensory input (cf. van Dongen-Boomsma et al., 2010). Auditory networks may be activated even when visual networks are passive; as such, dissociating between baseline cortical arousal and baseline activation has empirical confounds (for a discussion, see Northoff, Duncan, & Hayes, 2010).

However, research paradigms which include other psychophysiological measurements have been informative in evaluating EC and EO conditions (Barry et al., 2007). The skin conductance response (SCR) is an autonomic nervous system (ANS) response mediated by the amygdala (LeDoux, 2000). In TD adults, skin conductance levels (SCL) correlate negatively to resting-state alpha activity in both EC and EO conditions; with lower SCL found during EC resting state and increased levels on opening the eyes, reflecting greater ANS response (Barry et al., 2007). In contrast, research with developmental disorders characterised by attentional deficits describe SCL hypo-arousal as well as attenuated alpha during EC (ADHD; Barry, Clarke, Johnstone et al., 2009). Research measuring SCL in adolescents and young adults with WS during task performance has demonstrated hypo-arousal compared with typically developing controls (Doherty-Sneddon, Riby, Calderwood, & Ainsworth, 2009; Plesa-Skwerer et al., 2008; Riby, Whittle, & Doherty-Sneddon, 2012), likely reflective of the structural and size abnormalities of the amygdala in individuals with WS (Reiss et al., 2004). Notably, two of these studies (Doherty-Sneddon et al., 2009; Riby et al., 2012) also included a ‘floor’ condition whereby the participants looked at the floor

without performing any goal-directed activity, thus providing a baseline measure of their SCL. In both studies, the WS group had numerically lower SCL at rest compared with the control group, indicative of underactivity in the ANS during an EO resting state. Other developmental disorders have inconsistent findings in SCL hypo-responsiveness (ASD, Riby et al., 2012; Stevens and Gruzelier, 1984; DS, Martinez-Selva, Garcia-Sanchez, & Florit, 1995; FXS, Cohen, Masyn, Mastergeorge, & Hessl, 2015; Miller et al., 1999). However, in light of the lack of significant findings between the WS and the CA groups in Chapter 6, incorporating ANS responses such as SCR measurements in future EEG research maybe a useful non-invasive resource to further elucidate how the interplay between EEG cortical hyper-arousal and ANS hypo-arousal in WS during EC / EO characterises group differences between resting-state conditions.

Whilst the results have provided a preliminary indication of the EC / EO resting-state profile in WS, as highlighted in the introduction of Chapter 6, evidence of functional connectivity between cortical regions is informative when dissociating between typical and atypical development (Wass, 2011). Specifically, the alpha and beta bands have stronger correlations with the dorsal attentional resting state networks (Mantini et al., 2007). Dorsal stream dysfunction is well established in the WS literature (Atkinson et al., 2006; Meyer-Lindenberg et al., 2004), with underactivity in parietal and visual cortices characteristic of the WS neuroanatomical profile (Mobbs, Eckert, Mills et al., 2007). Furthermore, there is evidence for atypical functional connectivity between other cortical–subcortical regions that can be associated with syndrome-specific behaviours in WS. For example, under-connectivity between the amygdala and

pre-frontal cortex is associated with social-cognitive processes (Meyer-Lindenberg, Hariri et al., 2005), and between the striatum and right inferior frontal gyrus (rIFG), thought to be reflected in their atypical inhibitory processing (Mobbs, Eckert, Mills et al., 2007). Analysis of functional connectivity was outside the remit for Chapter 6, however the findings from this study, coupled with evidence from existing research, indicate there is a gap in the literature which needs to be addressed in order to provide a cohesive understanding of the atypicalities in EEG in WS.

7.7 Variability and individual differences in the WS sample

There is much discussion in the literature regarding variability and individual differences within developmental disorders (e.g. Porter & Coltheart, 2005; Van Herwegen et al., 2011). Certainly, the issue of variability in the data has been raised throughout the thesis. Specific to the current programme of research, greater variability was observed in the WS group in the behavioural studies compared to the electrophysiological studies. Most notably, the numerically low variability in the upper-alpha band during the EC condition provides a preliminary suggestion that EEG variability in WS has a functional significance in the cognitive and EF profiles in WS. However, the research discussing the role of variability typically adopts a group perspective, whereby one group's mean variability is compared with that of other populations (Van Herwegen & Riby, 2015). Whilst this is highly informative, overall group data may mask within syndrome sub-group and individual differences (e.g. Nigg, Wilcutt, Doyle, & Sonuga-Barke, 2005). Seven of the nine adults with WS from the cohort in Chapter 6 participated in four of the experiments (data from one was omitted

from the Oddball task due to insufficient trials post-ERP processing), whilst six completed all studies of the thesis. This has provided an ideal opportunity to visually inspect individual differences across their behavioural and electrophysiological profiles, and provide anecdotal information regarding specific individuals whose profiles differ somewhat to the rest of the sample.

In the verbal and visual AM tasks (Chapter 2), participant 2's RT was faster during item recognition than the other participants. This resulted in chance performance for verbal item recognition but relatively good performance on visual item recognition. In the paired-associates tasks, participant 2's RT was faster in both domains. In the verbal paired-associates task, both hit and FA rates were at chance which suggests attentional disengagement, possibly exacerbated by task difficulty. In contrast, the hit and FA rates in the visual paired-associates task were high, thus suggesting a speed–accuracy trade-off. In the SART (Chapter 4), participant 1's FA rate was high despite comparable RT, which suggests greater inhibitory deficits possibly reflective of their propensity to respond. In contrast, participant 5's RT was the slowest out of the the sample in the verbal paired-associates task, but also had low hit and FA rates. Thus they were not able to benefit from this greater evaluation time in order to maintain sustained attention. In contrast, in the LoP task (Chapter 3), participant 5 again stood out as having a much slower RT but this did not reflect in notable differences in their hit rates compared to the other participants, possibly due to the lower task demands. However, as their hit rate to the new items was below chance level, they could not benefit from this longer RT in order to correctly reject unseen items.

Inspection of individual differences in the electrophysiological studies also suggested that specific atypical EEG profiles that may be related to performance in the behavioural studies. The Oddball task (Chapter 5) highlighted atypical activity in participant 5 with a tendency for a more centro-parietal P3a distribution, and a notable frontal P3b which was also greater in amplitude than the other participants. Thus, their slower behavioural RT in the LoP task may in part reflect these topographical distribution differences. Participant 1 had greater fronto-central N2 amplitude in response to the target in the Oddball task. This is noteworthy as the target N2 is usually characterised by a centro-parietal distribution, and considering the overall attenuated N2 found in results of the WS group in Chapter 5. However, atypically enhanced N2 has been observed previously in WS (Mills et al., 2000). The EC / EO paradigm (Chapter 6) also identified differential EEG activity in this sample. During EC, both participants 1 and 2 presented notably greater full- and low-alpha power and which was also widely distributed topographically. This is indicative of greater cortical inhibition, and contradicts their behavioural performance on the SART (though this may reflect differences between resting states and task-specific EEG activity). Greater power in the upper-alpha band was also observed in these participants, but this appeared to be localised occipitally. Participant 7's beta power was greater compared to the other participants, which was localised fronto-occipitally. No obvious individual differences were observed in the EO condition; however, there was a dissociation in topographical distribution in the beta band between participants 1 and 7, with greater frontal power for participant 1, and greater occipital power for participant 7. These individual differences in both the EC and EO conditions possibly reflect over-activity during resting states which may then

result in atypical attentional processing during task-relevant activity (SART). These suggestions need to be addressed with caution as this was based on visual inspection of the pattern of data, rather than via statistical analysis. However, from this small sample, it is possible to obtain an overview of specific individual behavioural and electrophysiological differences which are typically masked by group comparisons.

7.8 Group matching

A notable issue with developmental disorder research is the most appropriate method of group matching (as outlined in the General Introduction, *section 1.3.1*). In Chapters 2 (AM) and 4 (SART) the WS group's data were compared with TD adults matched for chronological age (CA), and a group of TD older adults (65s), whereas Chapters 3 (LoP), 5 (Oddball), and 6 (EC / EO) included CA-matched adults and children who were matched for verbal mental age (MA). It was noted in Chapters 2 and 4 that the 65s group were high functioning thus most likely not a representative sample. However, the inclusion of a control group of TD children in Chapters 3, 5, and 6 has demonstrated that both the behavioural and electrophysiological profiles observed in the adults with WS in the paradigms adopted here were not reflective of delayed development. This indicates that the cognitive and executive processes under investigation have developed with increasing age, thus this group of adults with WS presented behavioural and electrophysiological profiles reflective of their intellectual difficulties. More informative was the comparison between the WS group and the published research with other developmental disorders. It has been noted throughout the thesis that individuals with ADHD present many similar behaviour

characteristics / deficits in attention and inhibition as found in WS (Rhodes et al., 2011), thus the thesis would have benefited from an ADHD comparison group and should be considered for future research. This is emphasised by the research by Coghill et al. (2014) who found that, whilst boys with ADHD reported deficits across six neuropsychological domains including WM, inhibition, and RT variability compared to TD controls, these deficits appeared to be independent of each other. Moreover, impaired performance was only reflective of a small number of the sample, as the majority of the ADHD group's performance overlapped the TD group. The authors highlight that ADHD symptomology may be attributed to much wider spread of brain activity than typically discussed. Certainly, it is only with the inclusion of additional groups with developmental disorders that we can make suggestions about the syndrome-specific pattern of results presented here and allow us to understand any general performance characteristics associated with the presence of intellectual difficulties. Of note, comparison of WS with other developmental disorders such as ADHD, whilst informative to syndrome-specificity, also needs to consider categorical diagnoses using diagnostic tools compared with and along side parental reports (dimensional approach; e.g. Hudziak, Achenbach, Althoff, & Pine, 2007). Differences in treatment, including early parental interventions are important not only for early management of symptomology, but also in the subsequent longitudinal cognitive and behavioural outcomes for individuals with developmental disorders (Estes et al., 2015; Martel, Markon, & Smith, 2016; Paterson, Parish-Morris, Hirsh-Pasek, & Golinkoff, 2016; Pickles et al., 2016).

As previously noted, the inclusion of TD children especially in electrophysiological research paradigms, is problematic as their ERP profile reflects *developing* as opposed to *developed* neural processes (Karmiloff-Smith, 2013). EEG frequency distributions between adults and children may not be comparable, due to typically faster oscillatory firing rates in children than in adults (for a discussion, see Uhlhaas & Singer, 2011). The developmental profile of EEG oscillations is not complete until early adulthood (Uhlhass et al., 2010). Topographically, developmental changes occur faster in posterior regions than frontally (Niedermeyer & Lopes da Silva, 1999), whilst the reduction in the amplitude of oscillations is especially pronounced for delta and theta activity during childhood and into adolescence (Whitford et al., 2007). Specific to Chapter 6, low-alpha (8–10Hz) activity decreases, and theta activity is replaced by activity in the upper-alpha (10–12Hz) sub-band, up to 14 years of age (Gasser et al., 1988). Therefore, in research paradigms such as in the current thesis, alpha power in adults may be compared in error to theta power in children, depending on the age of the individual.

Similarly, in the ERP profile, a developmental pattern of brain activity is consistent throughout childhood and even into middle age (Mills et al., 2013). Maturation (decreasing amplitude) of the P3a typically occurs into late adolescence, though increases in P3a amplitude with age have been observed (Kihara et al., 2010), and subsequently increases with adult ageing; whereas the P3b is characterised with a non-linear decrease in amplitude but no change in latency with age (Stige et al., 2007). In contrast, the N2 appears to reach adult levels by approximately 9 years of age (Batty & Taylor, 2002). However, there

are domain-specific developmental processes in ERP maturation; for example, adult-like brain semantic activity has been observed as young as 7 years (Cummings, Ceponiene, Dick, Saygin, & Townsend, 2008), and at 10 years of age (Hahne, Eckstein, & Friederici, 2004). Furthermore, there are notable changes in this developmental trajectory from 5 years until 15 to 16 years of age, with the largest effects being observed in the younger end of this age range (Holcomb, Coffey, & Neville, 1992). See Sato et al. (2015) for an extensive study on developmental and child pathological comparison.

There were inconsistencies in the thesis regarding the standardised tests used for group matching purposes. Standardised FSIQ testing was omitted in Chapters 3 (LoP), 5 (Oddball), and 6 (EC/EO) due to the WS group's inverse profile of VIQ / PIQ scores in Chapters 2 and 4 (cf. Farran et al., 2010; also see the General Introduction, *sections 1.1.4* and *1.3.1*). The BPVS was included in Chapters 3, 5 and 6 to assess verbal mental age; though this was only administered to the WS and the MA groups, as only standardised up to the age of 16 years. Also, recent research (Purser et al., 2011) suggests that the BPVS over-estimates the lexico-semantic knowledge in WS. For consistency, future research should include an appropriate standardised test that can be administered to all groups, however this is in itself an issue because IQ assessments are developed and standardised on typically developing individuals and therefore struggle to accommodate the needs of individuals with developmental disorders, especially where a large dissociation across cognitive domains may exist. These data may also be beneficial in explaining the pattern of results. For example, in Chapter 5, there were no significant correlations

between the P3b / target N2 latency and behavioural RT in all three groups. This is unusual as significant correlations between N2 / P3b latencies and behavioural RT typically found (Polich, 2007), though not consistently (see Van der Molen et al., 2012, who also found no such correlations in both TD individuals and adults with FXS). Scores from an appropriate standardised test could also be used as a covariate during statistical analysis, thus providing a clearer picture of the behavioural, EEG / ERP, and variability profiles between individuals with WS and control groups.

7.9 Future directions: converging EEG / ERP and behavioural methodologies

Suggestions for future research have been outlined in detail throughout this chapter. However, the methodologies adopted here were analysed independently and suggestions made accordingly. Future research with WS would benefit from greater research endeavours which combine behavioural and electrophysiological methodologies. For example, EEG / ERP investigation of the attentional blink (AB) in WS would be complementary to the results from the SART (Chapter 4), Oddball (Chapter 5), and EC / EO (Chapter 6) paradigms. This paradigm requires shifting attention from one stimulus to a second stimulus within a short temporal window. In order to encode the second stimulus, the participant needs to successfully disengage from stimulus 1 and allocate attentional resources to stimulus 2. Thus, anomalous attentional processes can be indicative of deficits shifting between the allocation and the disengagement of attention, evidenced by impaired accuracy detecting stimulus 2 and / or longer durations between stimuli presentation. To date there is one known behavioural

study which has adopted the AB paradigm in adults with WS (aged 20–59yrs; Lense, Key, & Dykens, 2011), and found overall attentional impairments, evidenced by significantly poorer target detection as expected, and also greater difficulty disengaging and re-engaging their attention between stimuli. In contrast, Mason, Humphreys, and Kent (2005) found no difference in magnitude or duration in children with ADHD compared to age-matched controls, though they reported numerically greater errors indicative of deficits in sustained attention. The EEG / ERP research focusing on temporal dynamics of the AB phenomenon in TD individuals has linked greater alpha desynchronisation with greater blink magnitude (MacLean & Arnell, 2011), whilst the P3 component is attenuated in response to target 2 when target 1 is masked (Brisson & Bourassa, 2014). In light of the EEG / ERP profiles described in the thesis, this paradigm is ideally suited to follow on from the results from both the behavioural and electrophysiological studies here.

Similarly, the alpha and beta bands were analysed in the thesis due to their functional association with attentional and inhibitory processing. However, recent research identifies functional significance in the fronto-central theta band with early attentional processing, and centro-parietal delta with later controlled cognitive processes, and with greater sensitivity than the N2/P3b respectively (Harper, Malone, & Bernat, 2014). Furthermore, greater centro-parietal power in the delta band is elicited in response to errors of commission but not correct responses, and this activity can be dissociated from error-related mid-frontal theta (Cavanagh, Zambrano-Vazquez, & Allen, 2011; Yordanova, Falkenstein, Hohnsbein, & Kolev, 2004). Considering the habituation of the P3a to repeated

stimuli (Courchesne et al., 1975), future research would benefit from inspection of these EEG bands as they may help elucidate differences between individuals with WS and TD individuals, that are confounded in the ERP data (Harper, Malone, Bachman, & Bernat, 2016). It should also be emphasised that much of the ERP / EEG research now uses more sophisticated analysis of the functional connectivity between cortical regions. Thus future paradigms should also include these methods, as this provides a more comprehensive investigation of similarities and differences in the neurocognitive profile of WS.

7.10 Role of neurotransmitters in the EF profile of WS

A further area which is under-researched in WS is the role that neurotransmitters play in the atypicalities observed in executive processes discussed in the thesis. An examination of dopamine concentrations highlights the important link between these networks and EF, specifically in the regulation of behavioural inhibition (Heitland, Kenemans, Oosting, Baas, & Böcker, 2013; Swanson et al., 2007). Notably, the P3a ERP component has been linked to dopaminergic / frontal processes (Polich & Criado, 2006; Riby, 2013). In TD individuals, there is a positive relationship between behavioural response inhibition and striatal dopaminergic (D2) receptor availability (Ghahremani et al., 2012), which is attenuated on ingestion of dopamine antagonists (Kähkönen et al., 2002). In contrast, the neurodevelopmental disorders literature has linked aberrant dopamine levels in fronto-striatal pathways with deficiencies in early sensory processing and executive function in ADHD (Madras, Miller, & Fischman, 2005; Monchi, Petrides, Strafella, Worsley, & Doyon, 2006), and with the repetitive behaviours observed in ASD (Hamilton et al., 2013). To date, there is

no literature published that specifically investigates the function of dopamine deficiencies in atypical executive processes associated with WS; however an inability to inhibit involuntary movements has been tentatively linked with D2 deficiencies in cerebellar regions that network with the fronto-striatal pathway (Gagliardi, Martelli, Burt, & Borgatti, 2007).

Similarly, motor and behavioural deficits associated with atypical beta activity, have also been attributed in part to neurochemical imbalance in the neurotransmitter *γ*-Aminobutyric acid (GABA). Studies incorporating TMS methodology have linked successful stop trials, as opposed to go trials, with GABA-mediated inhibition in the primary motor cortex (van den Wildenberg et al., 2009). Disruptions in the GABA circuit have been observed in several developmental disorders including FXS (D'Hulst et al., 2006), ADHD (Edden, Crocetti, Zhu, Gilbert, & Mostofsky, 2012), Rett Syndrome (Chao et al., 2010), and ASD (Oblak, Gibbs, & Blatt, 2011). In ASD, atypical GABAergic interneuron development and connectivity in the prefrontal and temporal cortices (Casanova, Buxhoeveden, Switala, & Roy, 2002) is associated with disrupted excitatory / inhibitory balance in these regions (Levitt, 2005). Again, there has been little research focusing on GABA in WS; however a variation in the Dlx gene has been identified (Poitras et al., 2010), which is in part responsible for the migration of GABA into the cortex and is directly associated with the Gtf2i gene, one of the cluster of genes known to be depleted in WS (Bellugi et al., 1999; Osborne & Mervis, 2007). The link between behavioural performance and neurotransmitter imbalance is highly pertinent when considering the abilities of individuals with developmental disorders. For example, researchers have proposed that inhibitory

profile in ADHD may reflect insufficient neurotransmitter regulation rather than specific executive failures (Seargeant, 2000, 2005). Thus the question as to whether behavioural deficits in WS are due to atypical attentional / inhibitory processing or reflective of erroneous inhibitory modulation due to aberrant levels of modulatory neurotransmitters needs still to be addressed in much greater detail to inform our theoretical understanding.

7.11 Conclusion

To conclude, the thesis investigated cognitive and executive dysfunction in older adults with WS (aged 35+yrs), a cohort which, to date, has been notably under-researched in the developmental disorder literature. Throughout, the thesis has emphasised the role of atypicalities in the specific EF processes of attention and inhibition in the cognitive profile of adults with WS. Furthermore, there is a dearth of published studies which have used the methodologies adopted throughout the thesis. Therefore, this programme of research has added to the theoretical understanding of WS by advancing our knowledge of both the cognitive and executive deficits in older adults with WS, and the neuro-cognitive mechanisms which sub-serve these atypicalities, through under-utilised behavioural and electrophysiological research paradigms.

APPENDICES

Appendix i: Stimuli for the verbal associative memory task, Chapter 2

Appendix ii: Stimuli for the visual associative memory task and example images, Chapter 2

Appendix iii: Stimuli for the levels of processing task, Chapter 3

Appendix iv: Means and standard deviations for the Eyes Closed condition, Chapter 6

Appendix v: Means and standard deviations for the Eyes Open condition, Chapter 6

Practice stimuli		***Condition***		***Practice – item recog***		***Condition***	
RIBBON	SERMON	Unrelated		RIBBON	THREAD	Unrelated	
CONE	BAMBOO	Unrelated		PICNIC	SEWER	Unrelated	
ROD	SEWER	Unrelated		WIDOW	WIFE	Related	
AIRPORT	RUST	Unrelated		STUPID	BRAIN	Related	
MARRY	WIFE	Related		***Practice – paired associates***			
FIST	PUNCH	Related		CONE	BAMBOO	Unrelated	Intact
STUPID	THICK	Related		AIRPORT	SERMON	Unrelated	Rearranged
ELBOW	KNEE	Related		FIST	PUNCH	Related	Intact
Main stimuli				MARRY	KNEE	Related	Rearranged
Unrelated		**Unrelated**		**Related**		**Related**	
KETTLE	DANCE	ICICLE	DRAMA	SHED	CABIN	HAND	THUMB
BROOM	TEACHER	YOLK	ANGEL	CONVENT	CHAPEL	TONGUE	THROAT
MIXTURE	HILL	CURLER	PANE	MANSION	PALACE	HAIR	HEAD
BANK	KILT	HERMIT	SPATULA	GRAVE	MORGUE	KNIGHT	EARL
PROBLEM	WALL	FUSE	TUNIC	PRISON	DUNGEON	MONARCH	PRINCE
MILE	TOILET	WIRE	HEAP	CASKET	COFFIN	QUEEN	KING
BUBBLE	CARPET	COLONEL	FARE	DOCTOR	NURSE	LOBSTER	SHRIMP
ERROR	INSECT	NAPKIN	DEBT	AUTHOR	POET	SARDINE	HERRING
TEAM	STONE	MATE	BARGAIN	REFEREE	UMPIRE	MINNOW	MUSSEL
DANCER	LOAN	SNEEZE	MACHINE	SANDAL	SLIPPER	SONG	CAROL
SAUCER	TAIL	SHIELD	CIGAR	CAPE	HOOD	GOSPEL	CHOIR
TENT	WINK	NAIL	FARM	SOCK	BOOT	PSALM	HYMN
FOREST	INFANT	COLLEGE	TRUCK	SWORD	DAGGER	PUDDLE	POND
BUMP	WING	COIL	ESTATE	CLEAVER	BLADE	LAKE	RIVER
LOCKER	QUILT	SHOWER	POCKET	SPEAR	HARPOON	OCEAN	WAVE

Main response – item recognition

Unrelated				**Related**			
SNEEZE	MEASURE	BUILDER	CIGAR	SWORD	SPIKE	STAKE	HARPOON
NAIL	MISSILE	BRIBE	TRUCK	TONGUE	CHEEK	BRAIN	HEAD
COIL	SLEIGH	WHISKER	POCKET	KNIGHT	DUKE	LORD	PRINCE
SHIELD	PUPIL	PARTNER	MACHINE	SPEAR	STICK	CANE	DAGGER
COLLEGE	OVERLAP	PATTERN	FARM	HAIR	SKULL	CHIN	THROAT
SHOWER	CAFE	POSTER	ESTATE	MONARCH	RULER	VISCOUNT	EARL

Main response – paired associates

Unrelated – Intact		**Unrelated – Rearranged**		**Related – Intact**		**Related – Rearranged**	
KETTLE	DANCE	FOREST	WING	SHED	CABIN	CONVENT	PALACE
BROOM	TEACHER	BUMP	INFANT	CASKET	COFFIN	MANSION	CHAPEL
MIXTURE	HILL	LOCKER	DRAMA	DOCTOR	NURSE	GRAVE	DUNGEON
BANK	KILT	ICICLE	QUILT	CAPE	HOOD	PRISON	MORGUE
PROBLEM	WALL	YOLK	PANE	CLEAVER	BLADE	AUTHOR	UMPIRE
MILE	TOILET	CURLER	ANGEL	HAND	THUMB	REFEREE	POET
BUBBLE	CARPET	HERMIT	TUNIC	QUEEN	KING	SANDAL	BOOT
ERROR	INSECT	FUSE	SPATULA	SARDINE	HERRING	SOCK	SLIPPER
TEAM	STONE	WIRE	FARE	GOSPEL	CHOIR	MINNOW	SHRIMP
DANCER	LOAN	COLONEL	HEAP	OCEAN	WAVE	LOBSTER	MUSSEL
SAUCER	TAIL	NAPKIN	BARGAIN	PUDDLE	POND	PSALM	CAROL
TENT	WINK	MATE	DEBT	LAKE	RIVER	SONG	HYMN

Practice stimuli pairs		***Practice response***				
wardrobe	wheelbarrow					
table	rake	***Item recog***	***Cond***	***Paired associates***		*Cond*
rubber	dummy	sunflower	Orig	table	wheelbarrow	Rearranged
bike	toy	compass	Orig	balloon	carseat	Intact
sunflower	newspaper	torch	New	wardrobe	rake	Rearranged
fork	compass	jetski	New	chocolate	chicken	Intact
balloon	carseat					
chocolate	chicken					
Main stimuli				***Main stimuli***		
spade	rugbyball			flowers	drum	
donut	book			trumpet	plant	
plant	donkey			roller	cauliflower	
xmas tree	pizza			bulldozer	butterfly	
belt	cheese			hamster	stapler	
jar	football			elephant	pan	
cot	bin			candle	zebra	
piano	microwave			broccoli	violin	
guinea pig	lily			crown	washing	
flip flop	knitting			trombone	paddling pool	
bench	muffin			spoon	pin	
ambulance	highchair			blender	spanner	
canoe	icecream			handblender	watering can	
bucket	fruit			helicopter	golfball	
thread	jeep			screwdriver	stool	
scissors	tennisball			bag	pot	
chair	tennis racquet			hammer	wool	
ducks	toy			jug	key	

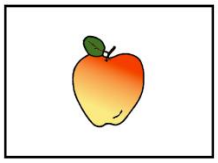
Main response – item recognition

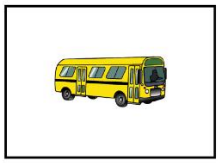
Item recognition	*Cond*	*Paired associates*		*Cond*
hoover	New	donut	book	Intact
golfclub	New	xmas tree	pizza	Intact
tent	New	cot	bin	Intact
phone	New	ambulance	highchair	Intact
teabag	New	thread	jeep	Intact
kettle	New	roller	cauliflower	Intact
carabiner	New	elephant	pan	Intact
tomato	New	handblender	watering can	Intact
hat	New	screwdriver	stool	Intact
glasses	New	bag	pot	Intact
tap	New	hammer	wool	Intact
rabbit	New	jug	key	Intact
rugbyball	orig	plant	zebra	rearranged
cheese	orig	piano	washing	rearranged
jar	orig	hamster	lily	rearranged
knitting	orig	chair	muffin	rearranged
canoe	orig	scissors	golfball	rearranged
fruit	orig	bench	tennis racquet	rearranged
toy	orig	trombone	plant	rearranged
flowers	orig	guinea pig	stapler	rearranged
bulldozer	orig	candle	donkey	rearranged
broccoli	orig	crown	microwave	rearranged
pin	orig	trumpet	paddling pool	rearranged
blender	orig	helicopter	tennis ball	rearranged

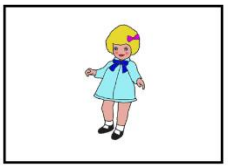
Animal	Cond	Fruit	Cond	Clothing	Cond	Vehicles	Cond	Toys	Cond	Tools	Cond	At recall
Mouse - Y	S	Apple - Y	S	Shirt - Y	S	Car - Y	S	Doll - Y	S	Ladder - Y	S	Replace
Pig - Y	D	Strawberry - Y	D	Skirt - Y	D	Aeroplane - Y	D	Ball - Y	D	Nut - Y	D	Replace
Horse - Y	S	Pear - Y	S	Dress - Y	S	Helicopter - Y	S	Kite - Y	S	Screw - Y	S	Keep
Tortoise - Y	D	Lemon - Y	D	Jacket - Y	D	Motorbike - Y	D	Bat - Y	D	Saw - Y	D	Keep
Elephant - N	S	Pineapple -N	S	Hat - N	S	Balloon - N	S	Top - N	S	Hammer - N	S	Replace
Lion - N	D	Cherry - N	D	Belt - N	D	Roller skate - N	D	Rugby ball - N	D	File - N	D	Replace
Cat - N	S	Grapes - N	S	Sock - N	S	Boat - N	S	Book - N	S	Axe - N	S	Keep
Dog - N	D	Pumpkin - N	D	Coat - N	D	Truck - N	D	Cart - N	D	Chisel - N	D	Keep
Deer	S	Orange	S	Tie	S	Bus	S	Whistle	S	Pliers	S	New
Cow	D	Tomato	D	Trousers	D	Sledge	D	Pram	D	Spanner	D	New
Sheep	S	Peach	S	Glove	S	Bicyle	S	Clown	S	Screwdriver	S	New
Bear	D	Banana	D	Shoe	D	Train	D	Swing	D	Nail	D	New

Appendix iii cont.

Chapter 3: Levels of Processing example stimuli







Appendix iv

Chapter 6: Means and standard deviations for the Eyes Closed condition

Full Alpha

	Hemi			Location			
	Left	Midline	Right	Frontal	Central	Parietal	Occipital
WS	1.496	1.426	1.329	0.975	0.682	1.175	2.836
SD	*1.164*	*1.033*	*0.985*	*0.749*	*0.547*	*1.014*	2.275
CA	5.371	5.033	5.325	3.198	2.1	4.283	11.392
SD	*5.83*	*5.217*	*5.248*	*3.509*	*2.19*	*4.668*	11.751
MA	14.466	11.875	13.081	6.692	4.983	12.976	27.911
SD	*16.836*	*12.657*	*12.456*	*10.033*	*4.571*	18.995	26.906

Low alpha

	Left	Midline	Right	Frontal	Central	Parietal	Occipital
WS	2.377	2.249	2.009	1.585	0.872	1.796	4.565
SD	*2.302*	*2.07*	*1.756*	*1.573*	*0.707*	*2.094*	4.363
CA	6.55	5.989	6.263	3.981	2.555	4.459	14.073
SD	*8.301*	*6.97*	*7.234*	*4.627*	*3.017*	*4.941*	17.762
MA	15.186	13.551	14.541	7.93	6.051	16.212	27.51
SD	*16.064*	*13.628*	*14.301*	*11.186*	*6.58*	21.567	21.71

Upper Alpha

	Left	Midline	Right	Frontal	Central	Parietal	Occipital
WS	0.785	0.767	0.785	0.478	0.531	0.678	1.429
SD	*0.436*	*0.39*	*0.539*	*0.243*	*0.472*	*0.462*	0.976
CA	4.424	4.266	4.575	2.567	1.735	4.139	9.247
SD	*4.54*	*4.444*	*4.438*	*2.961*	*1.758*	*4.864*	8.807
MA	13.89	10.533	11.913	5.702	4.129	10.387	28.231
SD	*18.461*	*13.148*	*12.572*	*9.28*	*3.237*	17.397	35.045

Beta

	Left	Midline	Right	Frontal	Central	Parietal	Occipital
WS	0.664	0.561	1.15	0.491	1.218	0.497	0.96
SD	*0.555*	*0.291*	*2.394*	*0.365*	*2.645*	*0.464*	1.042
CA	0.508	0.447	0.529	0.372	0.367	0.417	0.824
SD	*0.3306*	*0.276*	*0.262*	*0.236*	*0.281*	*0.273*	0.451
MA	1.041	0.901	1.11	0.78	0.54	0.789	1.943
SD	*0.5886*	*0.55*	*0.648*	*0.536*	*0.366*	*0.632*	1.015

Appendix v

Chapter 6: Means and standard deviations for the Eyes Open condition

Full Alpha

	Hemi			Location			
	Left	Midline	Right	Frontal	Central	Parietal	Occipital
WS	0.755	0.83	0.696	0.648	0.426	0.715	1.212
SD	*0.621*	*0.79*	*0.569*	*0.653*	*0.237*	*0.942*	0.908
CA	1.539	1.63	1.618	1.185	0.81	1.649	2.74
SD	*2.193*	*2.573*	*2.326*	*1.69*	*0.951*	*2.582*	4.276
MA	4.301	3.66	4.436	2.957	3.011	4.386	6.174
SD	*5.225*	*3.589*	*4.781*	*3.307*	*2.672*	*5.941*	6.726

Low alpha

	Left	Midline	Right	Frontal	Central	Parietal	Occipital
WS	1.08	1.216	0.995	0.981	0.502	1.107	1.797
SD	*1.423*	*1.784*	*1.304*	*1.11*	*0.557*	*1.712*	2.094
CA	1.479	1.533	1.439	1.225	0.851	1.407	2.452
SD	*1.935*	*2.122*	*1.888*	*1.148*	1.041	*1.644*	3.581
MA	4.664	4.584	5.2	3.712	3.641	5.737	6.174
SD	*5.639*	*4.704*	*6.571*	*3.218*	*3.905*	*7.11*	6.443

Upper Alpha

	Left	Midline	Right	Frontal	Central	Parietal	Occipital
WS	0.496	0.472	0.458	0.381	0.366	0.401	0.753
SD	*0.16*	*0.151*	*0.172*	*0.184*	*0.202*	*0.167*	0.287
CA	1.588	1.707	1.761	1.153	0.777	1.842	2.969
SD	*2.428*	*2.948*	*2.679*	*1.833*	*0.911*	*3.199*	4.849
MA	4.01	2.92	3.826	2.354	2.508	3.305	3.195
SD	*4.984*	*2.831*	*3.423*	*2.584*	*1.694*	*4.212*	5.158

Beta

	Left	Midline	Right	Frontal	Central	Parietal	Occipital
WS	0.629	0.458	0.598	0.655	0.608	0.312	0.671
SD	*0.411*	*0.198*	*0.608*	*0.597*	*0.646*	*0.142*	0.494
CA	0.399	0.367	0.429	0.359	0.3	0.306	0.627
SD	*0.255*	*0.274*	*0.237*	*0.257*	*0.269*	*0.209*	0.411
MA	0.794	0.679	0.878	0.752	0.46	0.596	1.324
SD	*0.497*	*0.453*	*0.597*	*0.482*	*0.315*	*0.471*	0.862

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