The uneven profile of memory development in Down Syndrome

The Uneven Profile of Memory Development in Down Syndrome

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Declaration

I, Katharine Mary Ondine Hughes, confirm that the work presented in this thesis is entirely my own. Where information has been derived from other sources, explicit attribution is made. Dr Esha Massand, the acting post-doc on the project at the time, designed the paradigm used in Chapter 3. The paradigm used in Chapter 7 was adapted from (Richardson & Kirkham, 2004) by Dr Massand.

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Abstract

This thesis explores memory development in children with Down syndrome (DS) between aged 3 years and 9 months and 14 years and 5 months (N=43). While memory has been extensively explored in older individuals with DS, relatively little work has considered the development of memory in childhood in DS, in part due to the difficulty of assessing memory in individuals with lower levels of ability. The project was innovative in applying a mixture of original and pre-existing tasks to this population, in order to characterise a wide range of memory abilities at varying levels of cognitive demand. These abilities were initially compared between those with DS and typically developing individuals by age group, early childhood (3 years 9 months to 8 years 4 months) and late childhood (9 years 9 months to 14 years 5 months). Standardised tasks were used to produce mental-age equivalents and raw scores for verbal and non-verbal memory abilities (BPVS, BAS II pattern construction).

Study 1 examined object and object-in-place recognition using eye-tracking, using a low demand methodology that excluded few participants. Study 2 examined verbal working and long-term memory abilities overall, as well as learning and forgetting rates. Primacy, recency and mid-list recall rates were also analysed to shed light on strategies of encoding. Study 3 examined spatial working and long-term memory abilities, as well as forgetting rates. Study 4 examined multimodal associative immediate and delayed memory, using a spatial-auditory associative eye-tracking paradigm. Study 5 examined the relationships between sustained attention, inhibition, and sleep behaviour measures, as these faculties are implicated in the development of memory abilities. Finally, in Study 6, cross-sectional developmental trajectories were constructed for all memory measures to ascertain if base levels or gradients of change significantly differed, either with respect to chronological age or domain-relevant mental age measures, in comparison to a sample of typically developing children. Overall, the project charted the emergence of an uneven profile of memory abilities across childhood in DS.

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ABC: Adaptive behaviour composite
AD: Alzheimer's disease
ADHD: Attention deficit hyperactivity disorder
APP: Amyloid precursor protein
BAS 2: British ability scale (second edition)
BPVS: British picture vocabulary scale
CA: chronological age
CANTAB: Cambridge neuropsychological test automated battery
CBCD: Centre of brain and cognitive development
CBQ: Childhood behaviour questionnaire
DAS: Differential ability scale
DNA: Deoxyribonucleic acid
DS: Down syndrome
EATQ: Early adolescent temperament questionnaire
EEG: Electroencephalography
ID: Intellectual disability
IQ: Intelligence quotient
LonDownS: London Down syndrome (consortium)
LTM: long-term memory
MA: mental age
MLU: mean length utterance
MTL: Medial temporal lobe
N: sample size
OSAS: Obstructive sleep apnoea syndrome
PAL: paired associate learning
PFC: Pre-frontal cortex
PLT: Percentage looking time
PSE: Phonological similarity effect
PSQ: paediatric sleep questionnaire
RNA: ribonucleic acid
RCPM: Ravens coloured progressive matrices
SBAB: Stanford-Binet abbreviated battery
SBIS: Stanford-Binet intelligence scale
SD: standard deviation
SE: standard error
SRBD: sleep related breathing disorder
STM: short-term memory
STS: superior temporal sulcus
TD: typically developing
WLE: word length effect
WM: working memory
WS: Williams syndrome
VSE: visual similarity effect

Age is often discussed herein as 00:00, representing years: months

Chapter 1 Introduction

In this chapter, Down syndrome (DS) and its associated diseases are introduced, before the illustrating how DS presents a unique opportunity and thus the motivation for this study. Some limitations of the current literature are then introduced, to highlight the questions this thesis attempts to address. Memory itself, and theories that influence our understanding of memory are then introduced. The development of memory in typically developing (TD) individuals and individuals with DS, are then described.

1.1 What is Down syndrome?

Down syndrome (DS) is the most common genetic form of intellectual disability (ID) (Daily, Ardinger, & Holmes, 2000). The majority of DS cases are caused by the presence of an extra copy of chromosome 21, referred to as trisomy 21, or full trisomy 21. The presence of this extra chromosome occurs due to nondisjunction during meiosis in either the maternal (most frequently) or paternal (~4%) gametes (Hassold & Hunt, 2001). DS can also be caused by the presence of an extra portion of chromosome 21 that attaches to another chromosome e.g. chromosome 14; this mechanism is called a translocation error rather than non-disjunction, and causes partial rather than full trisomy, as illustrated in Figure 1.1. In both cases it is possible for only a percentage of the cells in a person's body to have extra genetic material, these cases are called mosaic DS. Mosaic DS is caused by uneven mitotic chromosome segregation in the very early stages of foetal development and accounts for around 1% of DS cases (Zhao et al., 2015). There is some evidence that mosaic DS is associated with reduced severity of cognitive impairment, which can result in reduced rates of DS diagnosis in early developmental stages (Fishler & Koch, 1991; Zhao et al., 2015). The difference

between mosaic and partial trisomy is that in mosaicism only a proportion of the human cells have either full or partial trisomy.

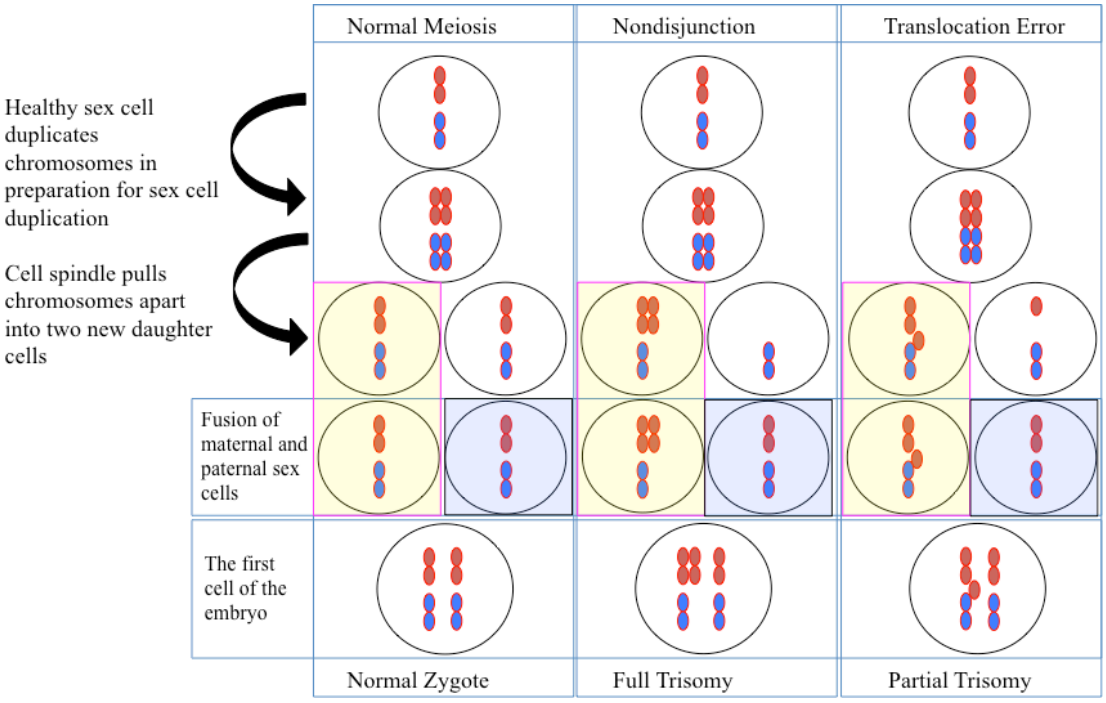

Figure 1.1 A schematic of the possible origins of chromosome abnormalities associated with Down syndrome. Gametes duplicate chromosomes to produce more gametes (oocytes or sperm). Although human cells contain 23 pairs of chromosomes, only two are illustrated here for clarity (red and blue). The gamete of one parent- illustrated in the yellow box- fuses with the gamete of the second parent- in the blue box- resulting in the zygote, the first cell of embryonic development.

Despite the classification of DS in 1867, relatively little is understood about the relationship between genotype and phenotype (Allen et al., 1961; Down, 1867; Lyle et al., 2009). The complexity of understanding this relationship is added to by the fact that the severity of the phenotype of people with DS is highly variable. For

example, it is possible for two individuals to have full trisomy 21 and yet present with completely different behavioural and cognitive profiles. Some people with DS are confined to a wheelchair, non-verbal and dependent upon others for the entirety of their lives. By contrast, others have gone on to graduate, be business owners, councilwomen, artists, musicians, actors, and sculptors. This huge variability makes DS a fascinating condition from both a genetic and psychological standpoint.

Features of the phenotype associated with DS are now presented along with altered disease risk profiles, followed by the motivation for this thesis. Some issues with the literature are outlined, followed by the ways in which the current thesis attempts to circumnavigate and address these issues.

1.2 The Down syndrome phenotype

DS is associated with many characteristic physical and cognitive features (Korenberg et al., 1990). People with DS are typically of reduced stature, with shorter necks, smaller heads and flattened back of head (Korenberg et al., 1990). Reduced muscle tone, delayed motor development and hypermobility are consistent features of DS (Korenberg et al., 1990). Hands and feet are typically shorter and wider. The big toe is sometimes further from the other toes with what is called a “sandal gap”. Similarly, DS is associated with a single “simian” palm crease, although these last two features occur in a minority of DS cases and are also found in some TD individuals (Devlin & Morrison, 2004). Facially, DS is associated with smaller ears, mouth and nose with a flattened nasal bridge (Korenberg et al., 1994). Epicanthal folds (single eye crease) are seen in around 60% of DS cases, although these are also found in some TD individuals, including those of East Asian origin. While it is stereotyped that people with DS have large tongues, there is no

clear evidence for this; rather the tongue appears large because of a reduced jaw size (Hennequin, Faulks, Veyrune, & Bourdiol, 1999; Hoyer & Limbrock, 1989). It is also possible that the tongue extends from the mouth due to poor muscle tone in cheeks and tongue, resulting in an open mouth and tongue protrusion (Carlstedt, Henningsson, & Dahllöf, 2003). Dental abnormalities are not uncommon, with teeth coming through in unusual orders and positions, also related to the reduced jaw size (Shapira, Chaushu, & Becker, 2000).

One of the common misconceptions about people with DS, is the homogeneity of the population. The majority of phenotypic features commonly described as characteristic of the DS phenotype are in fact highly variable. For example, people with DS are often referred to as having ID (Patterson, Rapsey, & Glue, 2013). In reality the level of ID ranges from mild to severe, and the percentages of individuals in each bracket changes over the lifespan (Nagumo, 1994; Roizen & Patterson, 2003). Variability in intelligence quotient (IQ) is observed both across the general population with DS and within specific sub-groups. For example, assessing individuals with DS aged 6 weeks to 21 years with the Leiter International Performance Scale (LIPS) showed females had better IQ outcomes than males (females: M=47, SD=15.6, males: M=37.5, SD=15.8), with profound ID outcomes seen in 10% of females compared to 24% of males (Carr, 1988; Määttä, Tervo-Määttä, Taanila, Kaski, & Iivanainen, 2006). Those with sleep disorders have lower IQ than those without, as assessed by the KBIT-2 (sleep disorders: M=43.84, SD=6.18, without sleep disorders: M=48.92, SD=10.65) (Breslin et al., 2014). Overall, although the mean IQ is significantly lower in individuals with DS, the range is comparable to the range seen in TD individuals in both childhood and adulthood (Carr & Carr, 1995; Tsao & Kindelberger, 2009).

These findings represent the importance of considering individual abilities, rather than generalising across populations.

1.2.1 Diseases in Down syndrome

People with DS are at increased risk of childhood leukaemia (2.1% increased risk), but are protected from solid cancers, which occur at half the expected rate (Hasle, Clemmensen, & Mikkelsen, 2000; Hill et al., 2003). Heart defects are common in infants, especially the atrioventricular septal defect, seen in around 40% of DS neonates (Freeman et al., 1998, 2008; Weijerman et al., 2010). Gastrointestinal impairments are also common, as are sensory defects including hearing and vision problems (Kent, Evans, Paul, & Sharp, 1999; van Trotsenburg, Heymans, Tijssen, de Vijlder, & Vulsma, 2006). There is also an increased susceptibility to infections and infectious diseases, potentially due to an altered immune state, also implicated in increased risk of thyroid and coeliac diseases (Bittles, Bower, Hussain, & Glasson, 2007; Garrison, Jeffries, & Christakis, 2005). People with DS are at greater risk of mental health disorders such as depression, schizophrenia and bipolar disorder, than the general population, but less risk than individuals with other forms of ID (Määttä et al., 2006; Waldman, O'Connor, & Tennekoon, 2006). Co-morbid attention deficit hyperactivity disorder (ADHD) and autism are also seen in a minority of people with DS (Capone, Grados, Kaufmann, Bernad-Ripoll, & Jewell, 2005; DiGuiseppi et al., 2010; Kent et al., 1999).

1.3 Motivation for the study

As DS is caused by the presence of extra genetic material, every gene that is present in triplicate has the potential to be expressed differently than in the population with the typical chromosome profile. However, the relationship between gene copy number and expression is non-linear (Letourneau et al., 2014).

Although it might be expected that a third copy of a gene would result in 150% of the gene product being expressed, this is not the case. Some genes that are present in trisomy are expressed at higher levels than in disomic cells, but other genes are expressed at equal, or lower levels than in TD cells (Letourneau et al., 2014). The causative mechanisms in irregular expression of trisomic genetic information have not yet been identified, and certainly contribute to the complex and variable phenotype associated with DS.

One gene that is present on chromosome 21, and has significant health consequences, is the amyloid precursor protein (APP). APP is required for healthy development and has critical physiological functions, as has been demonstrated in mouse knock out models (Koike et al., 2012). But when APP is processed pathologically a product called β-amyloid is produced, which is implicated in the pathogenesis of Alzheimer's disease (AD).

AD is neuropathologically defined by the build-up of β-amyloid plaques and hyperphosphorylated neurofibrillary tau tangles (Braak & Braak, 1991). Research suggests that the build-up of the former causes the formation of the latter (Hardy & Higgins, 1992). Due to the presence of a third and extra copy of this gene in DS, there is the potential for more gene product, which in turn increases the amount of the protein that can be pathologically processed resulting in the AD brain pathology (Neve, Finch, & Dawes, 1988). Analyses of port-mortem adult and foetal DS brain tissue have shown that APP itself is not over expressed, but the expression of many proteins involved in the processing of APP are dysregulated, implicating the processing pathways in altering the risk of AD (Lockstone et al., 2007). Soluble amyloid substrates are already found in children with DS as young as 21 gestational weeks of age (Teller et al., 1996). Post-mortem studies have also shown that

between aged 30 and 40 years of age, the vast majority of individuals with DS display the brain pathology associated with AD (Lemere et al., 1996; Malamud, 1972; Wisniewski, Wisniewski, & Wen, 1985). By 60 years of age, 50% of people with DS present with the clinical symptoms of AD (Janicki & Dalton, 2000; Karmiloff-Smith et al., 2016; Lai & Williams, 1989). The mean onset of clinical symptoms is 47 years of age, and the incidence at this age is 90 times higher in the DS population than in the TD population (Alexander et al., 2016). However, even though the current median life expectancy of people with DS is 55 years, and some individuals live to over 70 years of age, at no point do 100% of the DS population display the symptoms of AD (Wilson, Jones, Weedon, & Bilder, 2015; Zigman, 2013). Some research has suggested this is due to differential expression of genes that moderate APP expression/ processing (Chapman & Hesketh, 2000). At a biological level (genome, proteome, epigenome, neurome), individual differences are altering the risk for developing clinical AD. It is also possible that the environment is interacting with these levels, and also affecting the risk profile of developing AD. These individual differences are another extraordinary aspect endorsing the study of DS as a unique and intriguing genetic disorder.

It should be noted that there might also be individuals in the general population who have AD pathology and do not convert to AD symptoms. Due to a scarcity of post-mortem brain analyses in healthy individuals, it is impossible to confidently suggest figures for this occurrence. Thus, the DS population provides the unique opportunity to study a cohort from birth that will all develop AD pathology and has a higher risk of developing AD symptoms than the TD population. This could enable identification of risk factors in early developmental

stages that might allow intervention and prevention of conversion to AD symptomology in both the DS and TD populations.

As a result of the observance that some individuals with DS do not convert from AD pathology to symptomology, a group of researchers in London designed a project to identify the individual differences resulting in this protective effect. This group was called the London Down syndrome (LonDownS) consortium, and the project commenced in 2013. The consortium was initially made up of five research streams:

1. Adult: Investigating people aged 16 to 60+ years with DS, with and without AD diagnoses, no exclusion criteria. Cognitive assessments, electroencephalography (EEG), demographic and questionnaire information collected

2. Infant: Investigating people aged 6 months to 5 years with DS, no exclusion criteria. Cognitive assessments, EEG, eye-tracking, demographic and questionnaire information collected

3. Mouse: Investigating the physiological and behavioural effects of transgenic mouse models of DS, AD, and DS/AD. Behavioural outcomes are compared with human research streams. Some novel experimental paradigms in this thesis are directly based on mouse model findings from this stream and other mouse models of DS in the literature outlined in Chapter 3 Visual and Visuospatial Short-Term Memory.

4. Genetic: Saliva and blood collected from all human participants involved in the study. Methods include genotyping on Illumina arrays of common variants and also of specific risk factor genes, i.e. APOE allele, DYRK1A mutations

5. Stem cell: Inducing stem cells from blood/hair samples taken from all human participants involved in the study. These are then induced into neurons and neuronal networks to analyse differences in gene expression and neural behaviour related to cognitive dysfunction and or dementia that is caused by trisomy 21.

The LonDownS consortium had a five-year plan to collect and analyse data regarding the effects of DS on AD propensity using multidisciplinary methods. However, there was an age gap in the design for this project between 5 and 15 years of age. Thus, this PhD project was designed to cover this age gap, and complement the data collected by adult, infant, and mouse model research streams. For this reason, when selecting methods and specific assessments there were constraints on research designs in order to best align the outcomes with these research streams. Research paradigms and assessments were selected for consistency with the larger project. However, the larger project is not considered within the current thesis.

To enable the project to complement the work of LonDownS, but also to be a PhD project in its own right, it was decided that memory would be the main focus of the thesis. Memory is a key cognitive function in typical development, and also implicated in the clinical presentation of AD. The assessments used in this study were designed to assess memory, and supporting cognitive abilities of attention and executive function. The initial direction of the LonDownS memory research was influenced by work done in mouse models of DS, where there is greater flexibility in the experimental manipulations the mice can be exposed to, and in genetic mutations that can be induced. Experimental work that was influenced by mouse model research is described within the relevant chapter (Chapter 3).

Theories of memory influential to the discussion in this thesis, and the development of relevant abilities that are not specifically addressed within experimental chapters in the TD population are now discussed. This is followed by a review of the literature on the two main memory formats assessed in this thesis, verbal and visuospatial memory, in the DS population.

1.4 Memory

In this section of the introduction the theory of memory used herein to discuss memory is described. Evidence for the development of memory abilities in early childhood is the presented. This is followed by a discussion of memory related features that are not explicitly assessed in experimental chapters, but are relevant to our understanding of abilities in typical development. A review of the literature on verbal and visuospatial memory development, the main focus of this thesis, in the DS population in then presented.

It should be noted that the aim of this thesis is not to critique different theories of memory structure or function, but rather to examine the development of specific memory measures. Whilst multiple theories of memory are referred to in the introduction, the majority of the work discussed herein is in reference to the Baddeley theory of memory (Baddeley, 1986). Therefore, although this theory is far from unanimously agreed upon, for example see (Atkinson & Shiffrin, 1971b; Cowan, Nugent, Elliott, Ponomarev, & Saults, 1999; Engle, Tuholski, Laughlin, & Conway, 1999), it forms the basis of our research discussion in terms of the conceptual framework and therefore is the focus of this introduction. Within this theory there are three different storage systems of memory as temporally defined; short-term (STM), long-term (LTM) and working memory (WM). Others have described systems which are less explicit about the structure or function of WM,

although intermediary systems between STM and LTM stores are generally agreed to exist, sometimes described as an extension of the STM system (Atkinson & Shiffrin, 1968).

Memory is one of the most fundamental human cognitive functions, enabling us to adapt to the changing environment based on our previous experiences. Memory faculties allow us to convert immediate experiences into long-lasting memories and understanding of the world we live in. Memory facilities are essential for language learning and the development of other socially necessary skills such as the perception of others' motivations (Adams & Gathercole, 2000; Baddeley, Gathercole, & Papagnano, 1998; Nelson & Fivush, 2004). The construction of a personal framework through which to interpret the world is essential for cognitive development of memory and non-memory systems, and arguably required for the evolution of human sentience and consciousness (A. L. Brown, 1975). An illustration of the need for this personal framework is the majority amnesia experienced by humans until around 4 years of age (Eacott & Crawley, 1998). Once a sufficient framework is in place, humans are able to start encoding episodic memories regularly (N. S. Newcombe, Lloyd, & Ratliff, 2007). Some memories from prior to this age escape the amnesia and are successfully stored and retrieved in later life. These are usually either extremely rare, emotionally salient events, or regular and repetitive events (Cordón, Pipe, Sayfan, Melinder, & Goodman, 2004; Pillemer, Picariello, & Pruett, 1994). Even in these cases, it is difficult to determine how genuine these memories are, or how much they are due to hearing the story or seeing photos of the event. These occasionally occurring memories suggest that in typical development, between birth and four years of age, humans are collecting information that forms their personal framework through which to view the world.

The scarcity of memories during this period suggest memory is a framework-dependent process. Memory encoding appears to improve throughout childhood, adolescence and adulthood, due to the development of more refined methods of intentional information encoding (A. L. Brown, 1979).

Due the central nature of memory in our cognitive, social and communicative development, many academics have dedicated their careers to the characterisation of memory in typical and atypical development and degeneration (Baddeley, Buchanan, Thomson, & Buchanan, 1975; Farmer, Berman, & Fletcher, 1986; Logie & Marchetti, 1991). Rare cases where brain damage has resulted in memory dysfunction illustrate the essential nature of memory and its related structures. It was in 1953 that patient HM, an epileptic, had a portion of both hippocampi removed with the intention of reducing his seizures. Following this, HM was unable to store any new memories and suffered from retrograde amnesia, although his attention and WM were unaffected (Squire, 2009). From the day of his surgery patient HM lived in a world of around two years prior to that date; as he was never able to store new episodic memories, his personal framework was frozen in the past. This inability to store new information even extended to the recognition of words entered in the dictionary after 1953 (Corkin, 2002). This finding supports the role of the hippocampus in the development and maintenance of a personal framework.

1.4.1 Memory structure

Memory involves high degrees of communication between and within different cognitive areas. For simplicity and brevity, communication between domains is not discussed in detail here, as it is not the subject of this research project, but it is worth noting that no cognitive domain exists in a vacuum, and all

are more interconnected and inter-reliant than the literature is able to encompass. The three main features of the Baddeley theory of memory are now described.

1.4.1.1 Short-term memory

Immediate, or STM includes only the last few seconds of information (Gathercole, 1999). STM can store both verbal and visuospatial memory information, as well as other formats not discussed here, such as sensory information. In the Atkinson-Shiffrin model of memory, STM is less than one minute and TD individuals can hold 7±2 items in their STM (Atkinson & Shiffrin, 1971b; Kamiński, Brzezicka, & Wróbel, 2011). In the Baddeley model manipulation of data requires items to pass from STM to WM, which utilises the phonological loop, visuospatial sketchpad, central executive, and the episodic buffer (Baddeley, 1986). Authors frequently refer to systems within the WM as measures of STM, which can be confusing when studying the literature (Hitch, Woodin, & Baker, 1989; Jarrold & Baddeley, 2001; Purser & Jarrold, 2005). For the sake of clarity and consistency in this thesis STM is only used if the assessment did not require active manipulation of the data or explicit instructions, and is immediately assessed. Any experimental paradigm that requires the participants to maintain and manipulate information or explicitly respond will be discussed in terms of WM, even if the assessments are immediately presented.

1.4.1.2 Long-term memory

LTM is a storage facility of indefinite length and requires encoding of information past the immediate recollection of those data. To examine this domain experimentally requires allowing an interlude of more than 15 minutes to pass between the stimulus presentation and its recall. LTM can store memories for hours

to decades; the more the memories are accessed the more securely the memory is stored (Ericsson & Kintsch, 1995).

Information can enter and be retrieved from this store both actively or passively, also referred to as explicit and implicit memory categories (Graf & Schacter, 1985). Explicit, or declarative, memories are conscious memories of events or facts, which are further divided into episodic and semantic memories. Episodic memories are the individuals' perception of events, whereas semantic memories are facts, not dependent on personal experience (Tulving, 1972). Implicit memories are unconscious procedural memories, for example, how to ride a bike or travel a familiar route. Implicit memories do not need to be actively recalled, the individual simply carries out these actions subconsciously (Roediger, 1990).

Commonly, the memory formats assessed experimentally are verbal or visuospatial, both of which can be stored in LTM. However, memories formed in non-laboratory environments are usually composed of more complex scenarios and multiple memory formats, including associative memory.

1.4.1.3 Working memory

WM maintains and manipulates information, and requires active attention of the individual. There is not a clear definition of timings involved in WM, but it is measured in minutes, not hours, thus any memories that are recalled hours after WM tasks are not due to WM, but have passed into, and are recalled from, LTM. WM overlaps with both LTM and STM, and there is passage of information between the three memory stores (Baddeley, 1986; Gathercole, 1999).

WM utilises the phonological loop and visuospatial sketchpad (referred to as slave systems), the central executive and the episodic buffer, to retain information (Baddeley, 2000). The episodic buffer is a limited capacity system capable of

binding information from multiple systems into singular episodic or associative memories (Baddeley, 2000). The central executive is less clearly defined, but is generally credited for higher function abilities within WM, such as attentional switching and exchanging data between different memory systems (Baddeley, 1996). When discussing or researching WM it is important to remember the multitude of additional cognitive mechanisms required for proper WM function. For example, WM requires inhibition and orientation to prevent attention being captured by irrelevant distractors (Unsworth, Schrock, & Engle, 2004). The phonological loop and visuospatial sketchpad are discussed further within verbal and visuospatial memory sections respectively.

WM is capable of storing verbal and visuospatial data due to its specialised slave systems. Other data formats are thought to be manipulated by the episodic buffer, a domain responsible for abilities that cannot be allotted to any of the pre-defined memory systems (Baddeley, 2000). It is understandable to assign functions that cannot be explained by pre-existing theoretical structures, to an undefined system. However, the weakness of this definition is the challenge presented in testing the nature and function of this system with its indefinite boundaries and classification.

1.4.2 Development of memory in the typical population

Whilst discussing the development of individual systems, domains, and formats, it is important to remember the global change in relationships between verbal and visuospatial memory function that occurs. Before about 4 years of age it appears there is no preferential method for memory encoding. However, from age 4 to 7 years, visual encoding of memory is favoured (Hitch, Woodin, et al., 1989; Palmer, 2000). In other words, if the stimulus form is ambiguous, in early

development visuospatial memory will be used to encode the stimulus. After a certain age, around 7 years, this is replaced by a preference for verbal, phonological encoding of stimuli (Palmer, 2000). TD adults preferentially verbally label all forms of stimuli, suggesting this is their strongest memory format. Visuospatial memory does not cease to function at this point, studies in adults show that when the phonological loop is interrupted or interfered with, recall abilities are better than would be hypothesised, due to the collaborative nature of different memory formats (Hitch, Woodin, et al., 1989; Hurlstone, Hitch, & Baddeley, 2014).

Verbal and visuospatial memory abilities are largely uncorrelated and fundamentally served by unrelated systems, with potential overlap or complementary activities occurring for specific functions (Alloway, Gathercole, & Pickering, 2006; Pickering, Gathercole, & Peaker, 1998). Overall, verbal STM abilities are more advanced than visuospatial across development, indicating a potential origin of the preference for verbal memory encoding in later stages of development (Isaacs & Vargha-Khadem, 1989). Verbal memories appear to be processed more heavily in the left hemisphere of the brain, whereas spatial memory processing activates the right hemisphere more (E. Smith, Jonides, & Koeppe, 1996). Although fundamentally and experimentally separable, these memory formats certainly overlap to some degree, as evidenced by the fact that demands on the verbal WM system can impair visuospatial WM span (Miles, Morgan, Milne, & Morris, 1996). The inverse is also seen, visuospatial system activation impairs verbal WM abilities (Lee & Kang, 2002).

The development of abilities that are not specifically discussed in experimental chapters, but contribute to overall abilities, are now reviewed. The development of components of WM, and the relevance of LTM are examined. STM

and WM abilities are often conflated both in paradigms and in the literature. Therefore, although the STM capacity for verbal and visuospatial information increases over development, the exact timelines of this are not separately described herein (Alloway et al., 2006).

1.4.2.1 Central executive

The central executive and other executive functions are thought to rely on the prefrontal cortex (PFC), a slow and late developing brain area (Miyake et al., 2000). Although the central executive has many supposed functions, both related and un-related to memory, here the focus is on memory related features. Central executive function is a balance between storage and processing capabilities, as theorised by Case et al. (1982). The theory is that storage capacities remain relatively constant across development, but processing requirements reduce with development, increasing efficiency. As processing demands diminish, more energy becomes available for other functions, increasing storage capacities and memory abilities (Case, Kurland, & Goldberg, 1982). According to this theory of balance, the storage abilities of the central executive appear to increase during development, due to the reduced load required to process more information. Complex WM tasks, such as backwards digit recall, are thought to require input or modulation from the central executive. The ability of TD individuals in these tasks improves between 6 to 15 years of age (Siegel, 1994). There is synchrony between structural changes in the frontal lobe, and the development of central executive abilities between the ages of 1, 5 and 10 years (Case, 1992). Simple examples of central executive control can be seen in very early developmental stages, therefore these features do not suddenly appear in school age children, rather they develop slowly in infancy, rapidly over childhood and have reached adult levels by adolescence (Diamond &

Doar, 1989; M K Rothbart, Ellis, Rueda, & Posner, 2003). Therefore, across the chronological age (CA) included in this thesis, the prediction is that the abilities of the central executive overall should improve continuously, but not synchronously or linearly, across development.

1.4.2.2 Episodic buffer

The episodic buffer is proposed to require conscious awareness to be accessed and utilised (Baddeley, 2000). Therefore, individuals must be of a mental age (MA) with the capacity to consciously utilise memory abilities, which appears to be around 4 years of age (Alloway et al., 2006; Case, 1992; Palmer, 2000; Pickering et al., 1998). In addition to the need for consciousness, the episodic buffer is theorised to be responsible for merging data from the two slave systems of WM (Baddeley, 2000). Therefore, it is unlikely the episodic buffer is fully functioning until these two systems are also functional. This implies the episodic buffer may be present functionally from aged 4, but would not reach full capacity of functionality until the phonological loop and visuospatial sketchpad are developed, between 7 and 11 years of age.

1.4.2.3 Long-term memory

LTM is usually discussed in terms of implicit or procedural, and explicit or declarative, memory (Squire, 1992). Explicit memory is further comprised of both semantic and episodic memory forms. Semantic memory, for example, of word meanings and calendar months, has unidentifiable moments of learning. For this reason the development of this form of LTM is not well characterised. The phenomenon of childhood amnesia is thought to be due to an inability to appropriately store memories due to insufficient life experience (Eacott & Crawley, 1998; Nelson & Fivush, 2004). From around 4 years of age, the basic framework of

experiences is developed enough to house and store new memories appropriately (Nelson, 1993a, 1993b; Pillemer et al., 1994). There is also evidence supporting the theory that the more traumatic or unique an event is the more likely it is to be remembered, although this is a U-shaped curve with rarity on the x-axis, with mundane and very regular events also better remembered than uncommon but non-emotional events (Hamond & Fivush, 1991; Ornstein, 1995).

Tasks such as delayed imitation demonstrate that long before the development of 4-year-old memory abilities, individuals are capable of learning and remembering non-verbal sequences for many weeks (Bauer, Hertsgaard, & Wewerka, 1995). Memory for meaningless sequences or events appear less well remembered than more salient, meaningful sequences, although some studies have found contradictory evidence (Bauer, Hertsgaard, & Dow, 1994; McDonough & Mandler, 1994). Therefore, findings in early memory function appear controversial, but it appears that the more the individual is directly involved in the event, and the more unique it is, the more likely it will be stored in LTM. Although evidence directly assessing the development of LTM is scarce, overall the capacity of LTM appears to increase until old age, when it decreases again.

1.4.3 Sleep and memory

Sleep, one of the fundamental features of human existence, is essential to many cognitive functions, both throughout development and across the life span. It is essential for the homeostasis of neural networks and the encoding and retrieval of memory. Even in fancy, napping results in better LTM retrieval (Hupbach, Gomez, Bootzin, & Nadel, 2009). Age 7 to 14 years children show strong positive effects of sleep on a variety of memory measures, including word pair learning and episodic memory encoding (Backhaus, Hoeckesfeld, Born, Hohagen, & Junghanns, 2008;

Henderson, Weighall, Brown, & Gareth Gaskell, 2012; Wilhelm, Diekelmann, & Born, 2008). Sleep problems have been associated with both impaired memory function, and overall reduced quality of life, highlighting the importance of good quality sleep across development (A. G. Thomas, Monahan, Lukowski, & Cauffman, 2015). For these reasons the effect of sleep on memory function will be examined within this thesis.

1.4.4 Summary

Overall, in typical development it appears that the majority of memory skills are present in their most basic capacities by age 4. Between 4 and 18 years, different domains develop at different speeds, and of course there will be individuals differences in developmental trajectories. Based on literature that will be addressed in the experimental chapters, the generalised development of memory systems are theorised to follow the trajectory of development outlined in Figure 1.2.

Although much of the literature is unclear or contradictory on the use of STM, WM and LTM terminologies, within this thesis the terms will be used as follows: LTM is used to describe any memory assessed after a 15-minute interval; WM is any memory within 15 minutes that requires active rehearsal or maintenance of data and STM is immediately assessed memory that does not require the maintenance of information or an explicit response, often in eye-tracking studies.

1.4.5 Development of memory in DS

There is less literature on memory in infants with DS than adolescents and adults. The reasons for this are threefold; firstly, recruiting and testing infants with DS is challenging. Secondly, there are few standardised tests that allow for infant

testing, especially those with delayed MA. Thirdly, those standardised tests that do exist are unlikely to be sensitive enough to capture the range of abilities associated with DS, which are usually below those of the CA-matched TD population. One study showed that infants aged 8-16 weeks with DS had reduced novelty preference for patterns and colours, which was interpreted as reduced memory for the original stimuli, compared to CA matched TD participants (Miranda & Fantz, 1974). Between the ages of 17-29 and 30-40 weeks there were no significant differences for novel pattern recognition between groups, but the difference between DS and TD individual performance for colour stimuli persisted (Miranda & Fantz, 1974). With faces, the youngest and oldest groups were TD comparable, with the middle group displaying a developmental delay, whereas when testing element arrangement recognition the DS groups were delayed at all ages compared to controls (Miranda & Fantz, 1974). Overall, by 5 months of age, DS infants recognise novel multidimensional patterns as well as TD infants and at 8 months the same applies for faces (Miranda & Fantz, 1974). Some authors have suggested memory in people with DS is unimpaired at 3 months old, whereas by 9 months the results are more variable and associated with cognitive development (Ohr & Fagen, 1991, 1994). The outcome of these somewhat dated studies appears to be that some features of memory improve typically over infancy, whereas others improve at a slower rate, illustrating the variability of different memory abilities in the DS population over time.

The hippocampus is essential for memory function. Some studies report correlations between CA and hippocampal volume in people with DS, demonstrating trajectory-associated variability in neuroanatomical changes (Śmigielska-Kuzia et al., 2011). The hippocampus and caudate nucleus are relatively

microcephalic by adolescence in people with DS compared to CA-matched controls (Jernigan, Bellugi, Sowell, Doherty, & Hesselink, 1993). This suggests a neuroanatomical basis for memory dysfunction in people with DS. However, clearly the volume of the hippocampus itself is not fully responsible for memory dysfunction in DS, other neural, developmental, and behavioural features most likely contribute to atypical development and outcomes.

In childhood, adolescence and adulthood, implicit LTM appears to function at a relatively high level, whereas explicit memory is MA delayed in both verbal and visuospatial formats, matched on logical operations or the L-M Stanford Binet intelligence scale (SBIS) (Lanfranchi, Toffanin, Zilli, Panzeri, & Vianello, 2014; Vicari, 2001; Vicari, Bellucci, & Carlesimo, 2000). There is evidence that visuospatial LTM is more delayed compared to verbal LTM when standardising by MA, compared to TD norms on the doors and people test (Jarrold, Baddeley, & Phillips, 2007). Studies of location memory have shown people with DS were delayed for their CA, but not MA, as long as the pictures were of imaginable objects, matched on L-M SBIS (Vicari, Bellucci, & Carlesimo, 2005; Zucco, Tessari, & Soresi, 1995). Therefore, LTM is impaired for MA in both verbal and visuospatial explicit formats overall, but that verbal LTM is better functioning overall, and within visuospatial function, location memory can be MA appropriate.

When reviewing the literature on verbal (Table 1.1) and visuospatial (Table 1.2) memory studies in infancy, childhood, adolescence, and adulthood, only papers with a TD group for comparison or with a longitudinal approach are included in the summary tables. Papers are presented in order of the CA range included in the study. The papers reviewed were selected by searching for the terms “memory”, “down syndrome” and either “verbal” or “visuospatial”, the focus was on papers

published in the last 10 years, but papers from before 2000 were included if they were frequently cited. Papers that focus on intervention, or review previous literature, rather than characterisation of development, were not included herein. Thus, although this was not a systematic review per se, it covers the majority of literature in the last 10 years that directly address the development of memory abilities in the DS population.

1.4.5.1 Verbal memory

The majority of studies of memory function compare participants with DS to MA-matched TD participants. The MA matching in tests of verbal memory is based on a range of different cognitive assessments, most commonly receptive or expressive language skills, non-verbal cognitive abilities, logical operation or variations on these common assessments. Some studies reported the full CA and MA range of all participants whereas others only reported the mean and standard deviation. Due to the volume of literature a review of studies carried out from infancy to adulthood is presented in table format in Table 1.1, followed by a summary of the implications of these findings. As visual data is reliably recoded into verbal data between around 5 to 7 years of age in the TD population, it is expected that in the DS population MA above 7 years will be more able to recode visual to verbal data, whereas below 5 years MA this ability is not expected to be present.

Table 1.1 A review of the studies of verbal memory in individuals with DS and main findings

CA range (years: months)	MA range	Study design	Group matching	Impairment found?	Form of memory assessed	Main conclusions	Reference
4:00-32:00	2-4:11	Cross sectional (N=61) and longitudinal (between 2 and 6 assessments) (N=147)	None-trajectory	_	Memory of sentences	Slight increase from 4 to 18 years, then decline into adulthood, greatest variability at age 18 but still not significant	(Couzens, Cuskelly, & Haynes, 2011)
6:04-17:03	3:00-7:10	Cross-sectional (N=54)	K-ABC	Yes	Auditory word span	Improved slightly with increased age, greater variability in controls	(Frenkel & Bourdin, 2009)
M=6, 7, 8	M= 12.23	Longitudinal (N=43)	WPPIS-block design	Yes at all time points, increasingly across time	Word span, sentence memory, non-word repetition. Also BPVS, picture naming, TROG-R, grammatical closure	Floor performance at 6 years, therefore trajectory only assessed7-8 years. Slower development in DS group in both measures	(Naess, Lervag, Lyster, & Hulme, 2015)

7-16	4:05-6	Cross-sectional (N=18) Tasks of increasing control demand	Logical Operations	Yes, increasingly across control levels	Forward, backwards and selective word recall, dual request word recall	Verbal memory impaired over multiple control levels. Control group performance was not altered over tasks	(Lanfranchi, Cornoldi, & Vianello, 2004)
7-18	*M* MA: 6:08 *M* PPVT=51.1	Cross-sectional (N=25) Supporting verbal memory with visual or visuospatial components	Two control groups matched on MA and receptive vocabulary MA=WISC and WAIS Receptive vocabulary= PPVT	Yes: digit, verbal-verbal Yes MA only: verbal-visual, visual-visual and visual-verbal No: spatial/ visual-visual	Forward digit; verbal-verbal; verbal-visual; visual-verbal, visual-visual, spatial/visual-visual	Adding a visual component eliminated impairment- authors argued this is of verbal memory, but task is purely visuospatial and requires no verbal or phonological coding. Significant correlations between digit span, verbal-verbal and visual-verbal abilities	(Duarte, Covre, Braga, & de Macedo, 2011)

8-19:10	MA = 4-7:04 Vocab= 2:06-7:03 Verbal= 3:03-5:03	Cross- sectional (N=20) Increasing control of verbal memory assessed	Two control groups matched on vocabulary and verbal skills Vocab= PPVT-R, Verbal= WPPIS-verbal	Yes, but no significant group by task effect	Word span, selective span, verbal double task, also WPPIS-performance and logical operations	Not caused by language impairment associated with DS. Evidence for impaired central executive. Correlations in DS group between word span and verbal abilities, verbal double task and logical operations	(Lanfranchi, Jerman, & Vianello, 2009)
8-23:03	2:05-10:05	Cross- sectional (N=45) increasing control of memory assessed	PPVT-R	Yes: significant impairment overall and task by group interaction	Selective word recall, verbal/visuospatial, verbal dual task. Also WPPIS-block design	Dual tasks (both verbal and visuospatial) were impaired compared to TD, evidence for impaired central executive deficit and verbal STM. DS group performance impaired on both within and between	(Lanfranchi, Baddeley, Gathercole, & Vianello, 2012)

						modality dual tasks	
8:02-11:03	3:06-5:00	Longitudinal (N=12) 3 visits within 18 months, final maximum age is 12:05	Non-verbal MA (LIPS)	Yes and did not improve	Digit and word span, also BPVS and expressive vocabulary test	Development of digit span and word span were significantly different between DS and TD groups. Vocabulary scores plateaued between times 2 and 3	(Hick, Botting, Conti-Ramsden, & Conti‐Ramsden, 2005)
10-18	4:08-6:11	Cross- sectional (N=30)	Logical Operations	Significant effect of group and of visual similarity across groups, no significant interactions	Picture span: control, phonologically similar, visually similar, long names	Evidence for visual over phonological encoding, in both groups from MA 5 onwards. Evidence for similar strategies at MA between TD and DS groups	(Lanfranchi, Toffanin, Zilli, Panzeri, & Vianello, 2014)
10:01-16:11	4:10-10:10	Cross- sectional (N=20) Recognition and recall of	None- 110 controls *M*	CA- yes, recall more impaired than	First and second names of familiarised faces	DS significantly impaired on BPVS and RCPM. Standardised	(Jarrold et al., 2007)

		verbal data	CA = 7:06	recognition BPVS- no RCPM- no	recalled from photo. Written names familiarised and then presented with distractors for recognition. Also BPVS and RCPM	probit scores used to calculate standardised residuals between DS and TD performance across CA, BPVS, and RCPM. Authors report as LTM but no mention of delay in assessment	
10:09-21:05	4:07-7:07	Cross- sectional (N=25) development of verbal STM	ABIQ	No, gradient of ability and intercept were not significantly different between DS and controls (4-9:02)	Word list recall, both span and number of correct trials	Raw scores converted to z-scores. Significantly improved over MA	(Carney, Henry, et al., 2013)
10:10-21:11	4:06-7:06	Cross-sectional (N=29)	Picture memory	Control condition significantly better than phonologically similar	Visually similar, phonologically similar, long named pictures	No significant difference between long names and visually similar images, suggesting the participants were verbally encoding and	(Danielsson, Henry, Messer, Carney, & Rönnberg,

						not impaired by rehearsal of longer words	2016)
M=13:11	*M=4:07*	Cross-sectional (N=14) Free recall of long/short lists, probed recall of long/short, similar/dissimilar lists	BPVS	Yes, long words less well recalled in free recall (WLE), and phonologically similar words less well recalled in probed recall (PSE) No: no difference in recall of long and short words in probed recall	Long vs. short words, Phonologically similar vs. dissimilar words, three words in a sequence and then probed recall	Overall, recency effect, no evidence the DS group were engaging in rehearsal, no affect of articulation rates, no primacy effect	(Jarrold, Baddeley, & Hewes, 2000)
M=14:03	*M=5:04*	Cross- sectional (N=19) Recall and recognition	BPVS	Yes	Auditory digit span, digit span with simultaneous visual support, either repeated verbally (recall)	Both recall and recognition benefitted from combined visual and auditory presentation of digits.	(Jarrold, Baddeley, & Phillips, 2002)

					or the initial list followed by another list which had to be judged "right" or "wrong"	Impaired verbal STM not primarily caused by auditory or speech-based production difficulties	
M=16:07	*M*= 9:01	Cross-sectional (N=15) explicit (recall and recognition) and implicit LTM	WISC-R, WAIS	No: stem completion, difference in recall of related/unrelated lists, rates of forgetting of word lists, Yes: total word recall, recognition, prose recall	Word list learning of related and unrelated words (5 immediate trials), only unrelated were assessed for recognition (delayed), stem completion (immediate), prose recall (immediate and delayed)	Evidence for primacy and recency effects in unrelated word list recall in DS group. Overall, LTM impaired in DS group, although implicit was not, no benefit from related item list	(Carlesimo , Marotta, & Vicari, 1997)
M=20	*M*=8	Cross- sectional (N=12) Decay of verbal information assessed,	RCPM	Yes, not affected significantly differently by rate of	Verbal WM (fast/ slow), also BPVS. Lower control assessments in test phase	No significant difference in decay of information between DS and TD groups matched on	(Purser & Jarrold, 2005).

	probed recall, lower control assessments also (N=16)	presentation	had less room for error by maintaining all stimuli on-screen (with distractors)	RCPM. In lower control recency effects observed- not seen in higher control recall task

Note. K-ABC= Kaufmann Assessment Battery for Children (Kaufman & Kaufman, 1983), WISC= Wechsler Intelligence Scale for Children (Wechsler, 1991), WPPIS= Wechsler Preschool and Primary Intelligence Scale (Wechsler, 2002), PPVT (-R)= Peabody Picture Vocabulary Test (-Revised) (L. M. Dunn, Dunn, Bulheller, & Häcker, 1965), LIPS= Leiter International Performance Scale (Leiter, 1940), BPVS= British Picture Vocabulary Scale, WAIS= Wechsler Adult Intelligence Scale (Wechsler, 2008) , RCPM= Ravens Coloured Progressive Matrices, (Raven, 1958) ABIQ= Stanford Binet Abbreviated Battery (Carvajal & Gerber, 1987), *M*= mean.

The overall picture to emerge from these studies is that, although from the CA of 7 to 21 years, verbal STM and WM appear delayed for MA; abilities improve with both CA and MA. Therefore, although the overall ability itself is not MA appropriate across multiple cognitive measures, there is some evidence it is capable of improving. Overall, studies show verbal memory is impaired compared to control groups matched on single cognitive measures or a wider range of composite scores, but a trajectory analysis showed that when compared to a younger CA group matched on combined verbal and matrices abilities only, the trajectory of DS verbal memory development is not significantly different from that of the TD group (Carney, Henry, et al., 2013). A longitudinal study of 6, 7 and 8-year-olds, sentence memory and non-word repetition ability became more impaired compared to the MA-matched group across CA (Naess et al., 2015). Therefore, verbal memory abilities, although increasing across childhood, appear to become continuously worse than the TD WPPIS-matched comparison group. A trajectory study of word list recall found that although the intercept of participants with DS between the ages of 10 and 16 years was significantly different to those of a younger but unmatched TD group, the trajectory of development was not significant different (Carney, Henry, et al., 2013). Therefore, although these skills in the DS population are developing later than the TD group, and the development is impaired from aged 6 to 8, between aged 10 to 16 years the trajectory can be comparable to TD development, although not at the same CA. Therefore, the expectation is that verbal memory skills should overall be delayed, but not over development. The literature also indicates that more meaningful results can be found by examining the data collected with more detailed or non-standard approaches.

1.4.5.2 Visuospatial memory

While visuospatial memory is composed of both visual and spatial components, the majority of studies made no distinction between these two cognitive domains. These abilities are referred to as visuospatial WM, STM, or LTM, depending on the storage domain the information is in. Some studies reported the full CA and MA range of all participants whereas others only reported the mean and standard deviation A review of the literature on visuospatial memory in the DS population from infancy to adulthood is presented in Table 1.2.

Table 1.2 A review of the studies of visuospatial memory in individuals with DS and main findings

CA range	MA range	Study design	Group matching	Impairment found?	Form of memory assessed	Main conclusions	Reference
4-32	0-7:11	Cross sectional (N=61) and longitudinal (N=147)	None-trajectory	-	Bead memory and pattern analysis	Steep increase from 4 to early adulthood, where bead memory scores decreased and pattern analysis plateaued, variability increased with age	(Couzens et al., 2011)
5-12:04	*M*=5:2	Cross-sectional (N=20) Pattern and load assessed	PPVT-R	Yes: main effect of group, due to exaggerated impairment in structured compared to random condition	Structured/ random simultaneous matrices free recall, also RCPM	DS impaired compared to TD, both groups better at structured but DS did not benefit from structure as much. Increasing the complexity of the matrix also affected the DS group more than the TD group	(Carretti & Lanfranchi, 2010)
5:06-20:06	*M*=4:07	Cross-sectional (N=48)	Pattern analysis, bead memory, mother's	Yes: pattern analysis No: bead memory The difference between	Pattern analysis, bead memory. Also PPVT-R and TACL-R, object	Bead memory developed slower than pattern analysis, analysed in 4-year age-groups. In DS	(Chapman, Schwartz, & Bird,

			education	bead memory and pattern analysis abilities was significantly greater in the DS than TD group and this exaggerated with age	hiding (immediate and delayed), expressive vocabulary, speech motor evaluation, immediate and delayed story telling	vocabulary more advanced than syntax	1991)
6:06-17:03	3:00-7:10	Cross-sectional (N=54)	K-ABC	No: Corsi block, yes: visual patterns	Corsi block, visual patterns task	Visual patterns ability improved with age similar to MA-matched TD controls. At low MA DS better than TD at Corsi, but worse at high MA. Both had comparable variability in DS and TD groups	(Frenkel & Bourdin, 2009)
7-17:11	PPVT *M*=6:00 RCPM *M*=5:09	Cross-sectional (N=34) spatial simultaneous and sequential	PPVT-R, RCPM	No: sequential, Yes: simultaneous	Pathway recall, selective pathway recall, position recall, selective position	No significant difference in processing speed (line and pattern comparisons), DS faster in WISC-R coding. Increasing the control had a	(Lanfranchi, Carretti, Spanò, & Cornoldi,

		recall at two levels of control each			recall. Also line comparison, pattern comparison, WISC-R coding	non-significant negative effect on DS abilities	2009).
7-18	*M* MA= 6:08 *M* PPVT= 51.1	Cross-sectional (N=25)	Two control groups matched on MA and receptive vocabulary MA=WISC and WAIS Receptive vocabulary=PPVT	Yes compared to MA matched group, no compared to receptive vocabulary matched group	Corsi span; verbal-verbal; verbal-visual; visual-verbal, visual-visual, spatial/visual-visual	Variance in abilities was similar in all groups, however, only 25-75 percentile of outcomes were included, potentially confounding results. Corsi span significantly correlated with visual-verbal and spatial/visual-visual abilities	(Duarte et al., 2011)
8-19:10	MA = 4-7:04	Cross-sectional (N=20)	Two control groups matched on vocabulary	No: low control, Yes: dual task	Pathways, starting position, visuospatial dual task. Also	More impaired compared to vocabulary matched TD group, than verbal skills matched group.	(Lanfranchi, Jerman, et al.,

	Vocab= 2:06-7:03 Verbal= 3:03-5:03	Increasing control of verbal memory assessed	and verbal skills Vocab= PPVT-R, Verbal= WPPIS-verbal		WPPIS-performance	Correlations in DS group between all tasks, logical thinking and WPPIS-performance, proof of relationship between executive control and intelligence	2009)
8-21	4-7:04	Cross-sectional (N=25) memory load and format are assessed, recall and recognition	FSIQ	No: spatial STM, strategy of visuospatial WM Yes: visual and spatial LTM, visuospatial LTM	Spatial STM (screen-based Corsi), visual LTM (recognition of familiarised abstract stimuli), spatial LTM (recognition of familiarised location onscreen), visuospatial LTM (PAL), visuospatial	TD significantly better at visual LTM than spatial, not seen in DS group	(Visu-Petra, Benga, Tinca, & Miclea, 2007).

					WM (free search of boxes to find hidden tokens)		
8-23:3	2:05-10:05	Cross-sectional (N=45) in creasing control of memory assessed	PPVT-R	No significant effect of group, but group by task interaction. Post-hoc showed significant impairment in visuospatial/verbal and visuospatial dual tasks	Selective pathways, visuospatial/ verbal, visuospatial dual task. Also WPPIS-block design	Increasing control of task impaired DS group more than TD group. DS impaired in both within and between modality dual tasks	(Lanfranchi et al., 2012)
8:02-11:04	3:06-5	Longitudinal (N=12) 3 visits within 18 months, final maximum age is 12:05)	Non-verbal MA (LIPS)	No comparison of overall abilities	Pattern Recall, BPVS, EVT	No significant difference in developmental trajectories of pattern recall abilities	(Hick et al., 2005)
9:05-	*M*=5:02	Cross-sectional	PPVT-R	No: sequential/	Recall of matrix	Overall, affect of presentation-	(Carretti,

17:11		(N=20) simultaneous and sequential presentation of patterned and random stimuli at increasing levels of cognitive load		simultaneous random Yes: patterned simultaneous	pattern presented on screen. Also RCPM	simultaneous better than sequential, and configuration-pattern better than random. Neither group was affected by pattern in sequential format. TD benefited significantly more than DS from pattern in simultaneous presentation. DS better overall in simultaneous task. Increasing load affected both groups equally in random task, but affected DS group more in pattern condition (within simultaneous presentation)	Lanfranchi, & Mammarella, 2013).
9:05-17:11	*M*=5:02	Cross-sectional (N=20) Patterned and	PPVT-R	Yes: main effect of group overall, pattern recall, from memory load of 4	Simultaneous structured/ random matrices verbal/	Both groups benefitted from patterned stimuli. Visuospatial WM equally affected by verbal or	(Lanfranchi, Mammarel

		random matrices at increasing load levels with verbal/ visuospatial interference recall assessed		onwards No: random recall	auditory interference. Also RCPM	visuospatial dual interference- implies both encoding techniques used at the MA included in this study	la, & Carretti, 2015)
10-18	4:8-6:11	Cross-sectional (N=30)	Logical Operations	No: no interaction between observed visual similarity effect and group	Picture span: control, phonologically similar, visually similar, long names	Reduced picture span in all conditions, with evidence for visual rather than verbal encoding preference	(Lanfranchi, Toffanin, Zilli, Panzeri, & Vianello, 2014)
10:01-16:11	4:10-10:10	Cross-sectional (N=20)	None- 110 controls *M* CA = 7:06	CA= yes, recall marginally more impaired than recognition	Recall and reproduction of shapes, recognition of	Scores converted as before. Across CA verbal worse than visuospatial, across BPVA and RCPM only visual	(Jarrold et al., 2007)

		Recognition and recall of verbal data		BPVS= yes recall, no recognition RCPM= no	familiarised doors among distractors	recall significantly worse. Authors report as LTM but no mention of delay in assessment	
10:09-21:05	4:07-7:07	Cross-sectional (N=25)	ABIQ	No, no difference in intercept of trajectory of ability over MA between DS and controls (4-9:02)	Corsi block recall	Raw scores converted to z-scores. Significantly improved over MA, and was not significantly different from rate of verbal ability improvement	(Carney, Henry, et al., 2013).
10:10-29:07	*M=5*:04	Cross-sectional (N=10) Visual object and visual spatial LTM	LM-SBIS	No: spatial (overall and by trial) Yes: object (overall and by trial, difference in ability increased over the three trials, apparently by no improvement in DS location recall)	15 objects presented, assessed with page of 4 items, target and 3 semantic distractors, target object must be identified (repeated 3 times). 15 common objects presented, each in a quadrant of	Effect of trial was significant in spatial recall, from 1 to 2 and 1 to 3 but not 2 to 3. DS group more able at spatial than object. Authors state LTM but all assessments were immediate	(Vicari et al., 2005).

					the page, assessed with object presented with blank quadrants, target quadrant must be identified (repeated 3 times)		
11-18	4-6:04	Cross-sectional (N=22) Tasks of increasing control demand	Logical Operation	No: low, low-medium Yes: medium- high, high	Memory for position, pathway forward and backwards, starting position, dual request selective task	Increasing the control of the tasks required eliminated the typical appearance of visuospatial WM and exaggerated the difference in group abilities	(Lanfranchi et al., 2004).
M= 14:03	*M=5:04*	Cross-sectional (N=19) recall and recognition	BPVS	No: recall, Yes: recognition	Corsi span	DS better than MA matched TD on Corsi, but impaired on recognition of Corsi sequences	(Jarrold et al., 2002)

		assessed					
M=20	*M*=8*	Cross-sectional (N=12, 16) Decay of information assessed, probed recall, at two levels of control	RCPM	No	Visuospatial WM (fast/slow). Lower control assessments in test phase had less room for error by maintaining all stimuli on-screen (with distractors)	No effect of rate, not significantly impaired compared to TD group. No evidence for rapid forgetting, recency observed in both low and high control task	(Purser & Jarrold, 2005).

Note. * = This MA was not the matching value, no MA was provided for matching value, only a raw score. PPVT-R= Peabody Picture Vocabulary Test-Revised, K-ABC= Kaufmann Assessment Battery for Children, RCPM= Ravens Coloured Progressive Matrices, PAL= Paired associate learning, WISC-3= Wechsler Intelligence Scale for Children, WPPIS= Wechsler Preschool and Primary Scale of Intelligence, FSIQ = Full Scale IQ, LIPS= Leiter International Performance Scale, EVT= Expressive Vocabulary Test (Williams, 1997), LM-SBIS= LM- Stanford Binet Intelligence Scale (Thorndike, Hagen, & Sattler, 1986), ABIQ= Stanford Binet abbreviated battery (IQ), TACL-R= Test for Auditory Comprehension of Language-Revised (Carrow-Woolfolk, 1985), BPVS= British Picture Vocabulary Scale, *M*= mean

The overall picture to emerge from these studies is that between 5 and 20 years of age visuospatial skills were MA appropriate across multiple measures of MA, and both visual and spatial abilities improve across development. Visuospatial STM was not delayed for MA and improved over developmental time (Hick et al., 2005). The relationship between visuospatial WM changed with the MA of the individual and the level of cognitive control required. At low MA participants with DS outperformed the K-ABC-matched TD participants (Kaufman & Kaufman, 1993). However, at higher MA the TD group outperformed the DS group on visuospatial WM as measured by Corsi block span (Frenkel & Bourdin, 2009). There was also an uneven relationship dependent on the level of cognitive control required. If the task demanded low levels of cognitive control the DS group were not significantly impaired in visuospatial WM abilities, whereas if the task demanded high levels of cognitive control the performance of the DS group was no longer MA appropriate in either sequential and simultaneous presentation of stimuli (Lanfranchi, Carretti, et al., 2009; Lanfranchi et al., 2004).

People with DS aged 10 to 30 years performed better at spatial than visual WM tasks (Vicari et al., 2005). This was also seen in participants age 6-17, where development of both abilities were not significantly different from K-ABC matched TD controls (Frenkel & Bourdin, 2009). In addition, age 7 to 18 participants were better at sequential than simultaneous visuospatial WM (Lanfranchi, Carretti, et al., 2009). A study comparing sequential and simultaneous random or structured matrices showed that the DS group were MA-appropriate in both simultaneous or sequential memory abilities in the random condition, whereas simultaneous structured matrices were relatively delayed for MA (Carretti et al., 2013).

Therefore, overall simultaneous memory skills were less proficient than sequential, although there were circumstances where both skills appeared equal.

1.4.5.3 Summary of memory development in people with DS

In WM participants with DS perform below MA levels in verbal WM tasks, but are MA appropriate in visuospatial WM tasks (Baddeley & Jarrold, 2007; Jarrold & Baddeley, 1997; Vicari, Carlesimo, & Caltagirone, 1995; Wang & Bellugi, 1994). Within the relative strength of visuospatial WM there is variability between sequentially and simultaneously presented stimuli, with participants aged 7 to 18 years displaying stronger WM skills in sequential than simultaneous tasks (Lanfranchi, Carretti, et al., 2009). Research has shown that the relationship between visuospatial WM in participants with DS and TD participants changes with the level of control required, where control is the cognitive effort or energy required to carry out a task. At low control levels DS and TD groups matched on various cognitive measures were not significantly different for visuospatial WM skills, whereas at higher control levels the TD children outperformed the DS group in both sequential and simultaneous visuospatial WM tasks (Frenkel & Bourdin, 2009; Lanfranchi, Carretti, et al., 2009; Lanfranchi et al., 2004). Thus, although many authors discuss the "strength" of visuospatial abilities in people DS, this is a generalisation, highlighting the importance of precisely describing the assessments and defining the formats of memory assessed (Yang, Conners, & Merrill, 2014). In addition to this, a study where participants were matched on both the British Picture Vocabulary Scale (BPVS) and Ravens coloured progressive matrices (RCPM), TD participants had marginally better verbal skills than visuospatial. This suggests that the relative impairment in verbal skills in the DS population may be driven by higher ability levels in MA-matched controls (Mosse & Jarrold, 2010).

Despite the overall discrepancy between verbal and visuospatial abilities participants with DS of CA 9 to 29 years displayed an Hebbian effect of repetition-driven long-term learning of both verbal and visuospatial stimuli, showing that learning can occur in both domains (Mosse & Jarrold, 2010). Hebbian learning is when repetitive exposures result in increased recall of information. This suggests that repetition itself could be an explanation for the relatively successful development of vocabulary compared to verbal memory and other verbal skills (Hick et al., 2005)..

There were more studies investigating visuospatial than verbal memory development. This could be caused by the fact that visuospatial memory is a relative strength of the DS population and researchers want to understand and capitalise upon this. Alternatively, it could be due to the fact that visuospatial has more facets to be unpicked than verbal memory, for example the temporal order. Studies of both verbal and visuospatial memory development have been carried out on comparable age ranges and sample sizes (N). The studies also MA match on a wide range of measures, and examine multiple different dependant variables. There are no marked differences between the research of the two memory formats, except for the formats themselves. Although having this range of matching methods and dependant variables is positive for increasing the understanding of more variables, it also limits the comparisons that can be made between studies. It would be useful to have a more cohesive approach to MA-matching, or which task to use as outcome measures for which cognitive features, as this would allow each new piece of research to add to the picture more collaboratively, rather than as stand-alone outcomes.

The relationship between ability level in memory measures and CA in both DS and TD populations is presented in Figure 1.2. As can clearly be seen, from the current literature reviewed above and in the relevant experimental chapters, the development of abilities is not comparable between the groups across development.

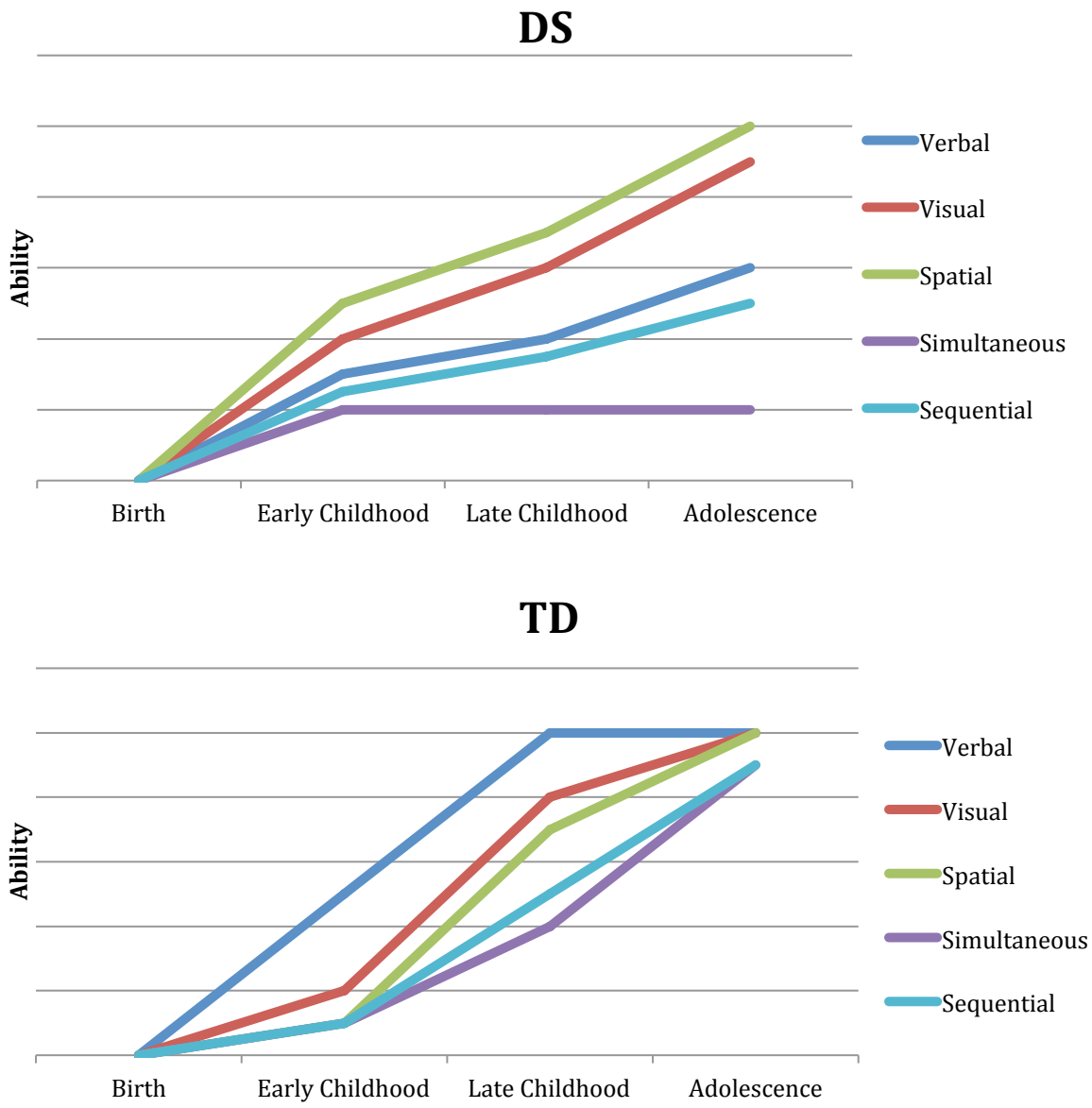

Figure 1.2 Proposed relationship between CA and memory abilities in the DS and TD populations, based on literature reviews

1.4.5.4 Limitations of the current literature

Due to the relatively high occurrence rate of DS, and the relative ease of early diagnosis, DS is a well-investigated genetic developmental disorder (Carney, Henry, et al., 2013). As a result, a great number of publications exist researching many features of DS in adolescence and adulthood. However, there are some limitations to the previous research that will now briefly be discussed. In the first instance, the majority of studies were carried out on small numbers of individuals with DS. This is partly due to the difficulty in recruiting large numbers of participants for experimental studies, which is even greater if the individuals are from an atypical group, as their presence in the general population is lower and they may be less available to take part in research. The small sample sizes (N) frequently reported in research of atypical populations are not necessarily an issue if the design and methods are reliable, and the research question is well defined, until one considers the age ranges included. Studies of people with DS frequently assess individuals with age ranges of a decade or more, and focused on group comparison between a DS group and a TD group matched on mean MA. To a developmental psychologist or neuroconstructivist, this is an undesirable way to assess development, as it averages across age and ignores individual differences and variability, which was previously mentioned as an frequently overlooked feature of the DS population (Karmiloff-Smith, 1998; Mareschal, Sirois, Westermann, & Johnson, 2007). Compared to the TD population, the cognitive profile of individuals with DS is more uneven. There is inter- and intra-individual variation across cognitive abilities over developmental time (Couzens, Cuskelly, & Jobling, 2004; Tsao & Kindelberger, 2009). A study of 195 participants with DS used both cross sectional and longitudinal analyses. Assessments on multiple measures were carried out between

1 and 7 times on the participants (Couzens et al., 2004). Pattern analysis, a measure of spatial processing and cognitive flexibility, displayed a wide range of developmental trajectories with increasing variability across age, whereas other skills such as memory for sentences showed almost no variability across the population or development (Couzens et al., 2011, 2004; Lanfranchi et al., 2012).

During infancy, childhood, and adolescence, a great deal of neural, behavioural and physiological changes occur in both the typical and atypical populations. Development is composed of many abilities with different gradients, and each individual may vary in the development of each trajectory. Therefore, it is desirable to have well-defined age-groups who are analysed separately, and if at all possible, assessed longitudinally. However, here again the literature encounters the issue of sample size. Having sufficient samples sizes of discrete age-groups over developmental time in an atypical population is a severe challenge. It is to avoid this issue that the usual approach of including wide age ranges has been applied.

1.4.6 Summary

Overall, a great effort has been made to characterise the developmental trajectory associated with DS. However, the field has been limited by a lack of cohesion in methods and aims. A limited number of studies have reported development of trajectories in fine-grained detail (Dykens, Hodapp, & Evans, 1994; Hick et al., 2005; Tsao & Kindelberger, 2009). The overall conclusion of these findings is that, although a great deal of work has been carried out investigating memory and phenotypes in DS development, there are several fundamental issues to be addressed. A primary concern is the large age ranges included in studies. To properly understand development, it should be examined in smaller groups of individuals within the closest possible age range to each other, or longitudinally

over development. Secondly, the majority of studies only investigated DS from late childhood onwards; leaving a developmental window that is unexamined. It would be desirable to have a cohort who could be studied from birth to adulthood longitudinally, but this is labour-intensive and therefore not attractive to researchers. Cross-sectional trajectory analyses appear the most appealing methodology for gathering the most accurate picture of memory development in the DS population.

The main aim of this project was to characterise the uneven memory profiles of participants with DS, and to ascertain if these profiles altered over development in a cross-sectional design. As the literature frequently fails to include children of a young CA, this study included participants of the lowest CA appropriate for the methods selected. People with DS with the youngest MA that could be included were also assessed, to explore the earlier stages of memory development. For this reason tasks with wide MA and CA inclusion criteria were selected. The focus of the study was the development of visuospatial and verbal memory, as these are the main memory formats the literature has investigated in people with DS. To expand our understanding of development, associative memory, as well as other memory-supporting cognitive abilities, were also assessed. Given the influential nature of cognitive control on the performance profile of people with DS, tasks with different levels of demand were included to see how this affected change in ability profile over development. For this reason, eye-tracking tasks were used, which require only eye gaze, to assess development of low control memory abilities. The changes in abilities were also compared to the change observed in the TD population, to characterise the differences in development of memory abilities over childhood in the two populations.

Chapter 2 Methods and Population Characteristics

2.1 Introduction

This chapter describes the recruitment, characteristics, and relevant demographic data of the participant sample, followed by a description of the study design and experimental methods. An overview of analytical techniques is also provided. In the description of each task the N of each participant group that completed each task is provided and the specific inclusion criteria, along with mean age-equivalents and other relevant outcome measures of each standardised task. The products of standardised tasks are analysed across CA at the end of the chapter as preparation for their use in correlation analyses in following chapters. Overall, MA-equivalents and group means are provided in Table 2.13. Birkbeck College Ethics Committee approved the study, prior to recruitment of participants (ethics certificate number: 151632). Ages are presented in the format of years: months.

2.2 Participants

The aim of this thesis was to examine change across age, to do this there are two potential methodological approaches that can be used. The first is to use the group as a whole and examine the trajectories of development across the entire range of ages included. The second is to split the sample into age groups and make comparisons between the case/control groups and age groups. Both these approaches have strengths and weaknesses. For example, trajectory analyses are more sensitive to cross-sectional age-related changes, but can be affected by individuals who perform at the minimum or maximum rates, as these scores skew the sample representation. Therefore, these individuals must be excluded from analyses, reducing the sample size and power. However, in the group method of

analysis the finer details of individual differences and variability can also be lost, but the method itself is more robust to more atypical data. Many studies that use longitudinal approaches still average group abilities to draw conclusions (Byrne, MacDonald, & Buckley, 2002; Hick et al., 2005). Therefore, in this thesis both methods are used to examine development in DS. The majority of previous literature used cross-sectional methods to group wide CA ranges, and did not examine development directly (see Tables 1.1 and 1.2). A minority of studies carried out longitudinal analyses, which did capture developmental change. Longitudinal methods were not realistic in the time frame of this thesis. Therefore, a cross-sectional approach was necessary, and to enable a developmental approach these individuals needed to be split into age groups. One previous study was able to split their participants by one-year intervals, but the sample size in the current study would not have permitted this approach (Tsao & Kindelberger, 2009).

Participants with DS were recruited between the ages of 3 and 15 years to complement the LonDownS age gap. To have the maximum N in each group, but also examine change across time between groups, the sample were split at the median age, being 9 years of age, into “early” and “late” childhood. Early childhood encompassed aged 3 to 9-year-olds, and late childhood included children aged 10 to 15-year-olds. Although some in this older group are adolescents, it was not possible to have a third group due to the limited number of adolescents, so the chosen divisions were used. The CDC splits middle childhood into ages 6-8 and 9-11, supporting a split at this age point (Middle Childhood, 2016). Further, in the context of memory treatment trials in DS groups have looked at early and middle childhood as important divisions for treatment approaches, helping us to map our findings onto those studies. Therefore, the majority of analyses will be carried out in a

group-dependent manner, with the final chapter including trajectory analyses where the data permits. Finally, the more robust/less sensitive group matching method was also employed because a number of the measures were novel or had not been applied to the DS population, and therefore the level of sensitivity across the age range was not known.

A total of 43 participants with DS responded to recruitment and were included in the research project. A further 32 TD participants of corresponding chronological age (CA) were also recruited and took part in the same assessments as the participants with DS, see Table 2.1 for a summary of participants in each group and age-group. Only TD participants without any diagnosis of developmental disorders or learning disabilities were included. A smaller TD N was considered sufficient for this study, as the main focus is the development over time of the DS cognitive profile. It was considered necessary to include some control participants for the novel methodologies and paradigms that were used. In the case that any assessment proved uninformative in regards to the DS phenotype, the inclusion of a TD population allows direct comparison in this subset of tasks and assessments.

2.2.1 Typically developing participants

Typically developing (TD) participants were recruited from the Centre for Brain and Cognitive Development (CBCD) database. Individuals were initially selected from the database that were in the appropriate CA range, and were not recorded as having any developmental disorders or learning disabilities. These families were contacted to register their interest in the study, and all those who consented to take part were included in the study. A phone call then took place to arrange dates and times for the visit, and complete demographic forms (see 2.2.4 Demographics). The demographic forms further confirmed that no individuals with

confounding disorders such as autism, epilepsy or mental illnesses were included. The total N of the group between 3:09 and 14:03 years of age was 32. A further five individuals between 2:06 and 3:06 years of age were also assessed to act as MA matches for the younger or less able participants with DS. One of these participants was excluded due to behavioural issues, making the overall N in the trajectory analysis 36. The overall N, with CA group means, minimum and maximums CA, and gender ratios are presented in Table 2.1.

2.2.2 Participants with Down syndrome

Participants with DS were recruited through charities and through the following local support groups Down Syndrome Extra 21, Downright Excellent, Down Syndrome Association and Down Syndrome International, and by word of mouth (http://www.extra21.org.uk, https://downrightexcellent.org, http://www.downs-syndrome.org.uk, https://ds-int.org). All families who consented to take part in the study and were willing to travel to London were included (N=43). A phone call then took place to arrange dates and times of visits, and to complete demographic forms (see 2.2.4 Demographics). Following the phone call, the first day of testing was carried out; at this point the study-specific exclusion criteria came into effect. The exclusion criteria were as follows; if the participant refused to engage in any of the assessments, despite the experimenters' perception that the participant was able to attempt the tasks. This excluded one participant. Three further participants with DS were not physically capable of completing many of the standardised tasks included in the protocol. Two of these participants (6:00, female; 12:03, male) had severe physical disabilities and were wheelchair bound, with little or no motor control over their arms, preventing participation in the Standardised assessments. A further participant (12:02, male) with severe

behavioural issues, potentially associated with comorbid ADHD/ Autism Spectrum Disorder diagnoses, attempted the majority of tasks but only for very brief periods, these results are included where possible, as they are representative of the range of the DS population. Both participants with physical disabilities were excluded from all Standardised assessments. All other exclusions, including the participant with co-morbid ADHD who was in late childhood, will always be explicitly mentioned in the discussion of each task administered.

All participants with DS who consented to take part in the study and did not fall in the exclusion criteria were included. This resulted in a group of 43 participants between the CA of 3:09 and 14:06 years. This group was split into two sub-groups, 3:09-8:03 years of age, and 9:09-14:03 years of age, which are referred to as early and late childhood, see Table 2.1. Although by 14 years of age individuals may be in adolescence, not late childhood, this issue was discussed and the purpose of having a third and separate group was deemed unnecessary and impractical with the N available (Dumontheil, Apperly, & Blakemore, 2010). Although it is possible that including adolescents in our analysis could result in a discontinuity with the younger individuals in the group, including individuals of the same CA in both groups should allow for these comparisons to be useful.

2.2.3 Participant group matching

The majority of previous studies have matched TD participants and participants with DS on some measure of MA, as shown in Table 1.1 and Table 1.2. However, this method of matching is not without its drawbacks. Given the well-characterised uneven cognitive profile associated with DS, matching on a specific measure has many potential outcomes. Depending on the task that the groups are matched on and the assessments carried out, the DS profile may appear very

different. For example, given that evidence suggests visuospatial WM is a relative strength of DS, matching on this measure might exaggerate the appearance of impairment in the DS group. This is because the visuospatial WM is TD MA-matched, but the TD cognitive profile is relatively even, meaning that if the cognitive measure is one that the DS group are impaired on, such as expressive language, then the delay between the TD and the DS population will appear exaggerated (M. S. C. Thomas et al., 2009). If the populations are matched on a more delayed feature of DS, such as mean length utterance (MLU) then the TD comparison group will be younger CA and therefore assessing another feature such as visuospatial WM, the DS group will appear relatively better than TD individuals. Not only do the relative abilities of the TD population in the matching and assessment measures have implications, but also if the two assessments are within- or between-domain assessments. For example, the implications are different if the populations are matched on a language measure and then assessed on attention or language abilities.

Therefore, the design of MA-matching between atypical and typical populations requires a great deal of theoretical and practical considerations. Due to the large literature using various MA matching techniques, I decided against this design. Some authors have not matched on MA, but have collected a wide CA range of TD participants, and compared the performance of each participant of the group as a whole to the development of the ability in the TD population matched for CA (Carney, Henry, et al., 2013; Couzens et al., 2011).

As the aim of this thesis is to examine the *development* of the uneven cognitive profile of memory in the DS population, it was decided that CA matching would be the best methodology. This method of comparing typical and atypical

populations necessitates that many measures will be significantly impaired between groups, but as it is the trajectories that are of interest, this approach was appropriate for our hypotheses. These analyses will also enable us to identify the relationship between the development of each measure in the DS and TD populations, as demonstrated in (M. S. C. Thomas et al., 2009). The four theoretical examples given in Thomas et al., (2009) are delayed onset, delayed onset and slowed rate, slowed rate, non-linearity and premature asymptote, these relationships will be considered in the analyses.

Table 2.1 Mean and range of CA of DS and TD groups in each age-group, overall N and N of each gender, including the extra group of younger CA TD individuals, in early childhood (3 to 9 years old), late childhood (10 to 15 years old)

	Extra	Early Childhood		Late Childhood	
Group	TD	DS	TD	DS	TD
N (female)	4 (1)	22 (13)	16 (10)	21 (11)	16 (8)
Mean CA in months (range)	36 (31-41)	73.55 (45-98)	71.19 (48-99)	147.95 (117-175)	139.63 (114-167)

2.2.4 Demographics

Demographic information was collected via the telephone in the initial phone call for all participants. The parent or caregiver of each participant was required to answer questions over the phone, and the researcher filled out the demographic forms. The Birkbeck Centre for Brain and Cognitive Development

form was filled out first, and collects basic parent and infant information, specifically on the birth of the participants, current medical requirements and language abilities. The Early Pre and Postnatal History form was then filled out, with information about developmental milestones of the participant, pregnancy, infant demographics of ethnicity, weight, height, and general questions about temperament of the participant. The final form was the Medical History form, which assayed presence of disorders in the participant, parents or other family members by asking about a series of diseases, disorders and conditions which fall under the following categories: Down syndrome, Developmental disorders, Sensory, Mental health, Allergies, Cardiovascular/Pulmonary, Head/Brain, Endocrine/Metabolic, Cancers, Gastrointestinal, Urinary/Bowel, Mouth/Teeth, Neck/Back/skin other. All three demographic forms were completed over the phone with a parent or caregiver and took between 30 and 120 minutes. A copy of all demographic forms can be found in Appendix A.

Comparing the DS and TD groups in terms of parental features, 66% of mothers of participants with DS were employed, whereas 81% of TD participant's mothers were employed. However, although 97% of father of participants with DS were employed, 88% of fathers of TD participants were employed. The level of education of these parents is presented in Table 2.2.

A commonly described risk factor for DS is maternal age. The average age of mothers of participants with DS at conception was 35 years, whereas the TD mother average age at conception was 31 years, which is a significant difference ($t(68)=4.26$, $p<0.001$, $\eta^2=0.059$).

Table 2.2 The highest level of education that mother and fathers of participants with DS and TD participants achieved

Qualification	Mothers		Fathers	
	% DS	% TD	% DS	% TD
<GCSE	0	3.23	5.41	0
GCSE	10.81	3.23	10.81	6.45
A-Level	16.22	3.23	0	3.23
Diploma	2.70	3.23	28.73	3.23
BA/BSc	45.95	41.94	27.03	38.71
MA/MSc	18.92	38.71	13.51	48.39
MD/PhD	5.41	6.45	13.51	0
TOTAL	100	100	100	100

2.3 Design

A large battery of tasks was used in the testing protocol originally designed to complement the LonDownS research questions and aims. This included many behavioural, eye-tracking, and EEG tasks that are not described here, but are outlined in Appendix B. The tasks included in this thesis are to provide a focus on memory as the central point of the research. Therefore, this thesis itself includes an eye-tracking measure of visual and visuospatial STM (Chapter 3). Immediate and delayed verbal memory are analysed to measure the WM and LTM verbal abilities and change over age in our population (Chapter 4). Immediate and delayed visuospatial memory are analysed as measures of WM and LTM visuospatial abilities and change over age in our population (Chapter 5). Associative memory is

assessed using an auditory-spatial paired associative learning (PAL) eye-tracking paradigm (Chapter 6). Experimental and questionnaire based measures of attention and executive function are also included as complementary to the healthy function of WM, and sleep measures are also discussed due to the influence of sleep on memory function (Chapter 7). Tasks are compared between groups, within the DS group within memory format, and then between group within memory format, with and without controlling for within-domain cognitive measures (Chapter 8).

2.4 Procedure

Although procedures varied between groups and across age ranges, generally all tasks were carried out in the order described here and outlined in Table 2.3. For both the DS and TD groups, the task order was adapted at the discretion of the experimenter to maximise the data obtained from each session. Both groups attempted all of the questionnaires, demographic forms, and eye-tracking tasks. The additional group of TD individuals between 2:06 and 3:06 years of age are only included in trajectory analyses (Chapter 8 Trajectory analyses of memory measures), not in the majority of experimental chapters.

Table 2.3 The order of tasks, day each assessment was administered to participants with DS, and what section of the procedure the tasks are described within.

Task Order	Day 1 or 2 of assessment in DS group	Procedure	Maximum time taken for assessment (minutes)
BPVS	1	Standardised assessments	30
Immediate verbal and visuospatial recall	1	Standardised assessments	10
Pattern construction	1	Standardised assessments	10
Recall of digits forwards	1	Standardised assessments	5
Picture recognition	1	Standardised assessments	10
Delayed verbal and visuospatial recall	1	Standardised assessments	5
Verbal Fluency	1	Experimental assessments	1
BREAK			
Memory of Object	2	Experimental assessments	3
Memory of Object-in-	2	Experimental	3

place		assessments	
Paired Associate Learning (Immediate test)	2	Experimental assessments	3
Gap-overlap	2	Experimental assessments	10
Paired Associate Learning (Delayed test)	2	Experimental assessments	1

2.4.1 Typically developing participants procedure

Following the consent to participate in the study and the phone call where the demographics forms were filled out, the TD participants came into the CBCD and the ethics of the study were explained to the parents/caregivers. This involved informing parents/caregivers that they had the right to withdraw at any time; with no need to give a reason and that it would not disadvantage them in any way. They were also told how the data are protected and that their anonymity is assured e.g. by each participant being labelled by number, rather than their name. When the study aims and ethics had been explained, and any questions were answered, parents signed the consent form, and the testing session commenced. This started with the tests described in the Standardised assessments section, followed by the experimental tasks. To control for fatigue affects this order was generally adhered to. Although a standard approach to control for this is randomising task order, it was decided that a common order would permit direct comparisons in this study, where a case-control design is used. Although it is possible fatigue is more severe in

the DS group, task order can be taken into consideration if analysing inter-task performance levels (Capone, Goyal, Ares, & Lannigan, 2006). Necessary breaks were provided between each session, and additionally if the participant expressed their fatigue. The complete battery of tests took between 2 and 3 hours, depending on behaviour, technical issues and number of breaks required. During the session two saliva samples were collected to analyse DNA and RNA, the subsequent analysis of which fell outside the scope of the current project. At the end of the testing session the participant was provided with a certificate of participation, and travel costs were reimbursed.

2.4.2 Participants with Down syndrome procedure

For the participants with DS a different structure was used for the testing protocol. Children with DS often have a reduced attention span and tire quickly (Määttä et al., 2006). In order to control for this, the session was split over two days. On the first day the experimenter visited the families at home and explained the ethics of the study. When the parents/caregivers had the study aims and ethics explained to them, had all their questions answered, and signed the consent form, the testing session commenced. During the home visit the participant carried out the Standardised assessments section of the study. This enabled the experimenter to assess the child's overall abilities and disposition and was used to tailor the approach taken on day two. This also helped the child feel more at ease with the experimenter, improving the quality of the data subsequently collected. This session lasted 1 to 2 hours, depending on behaviour and number of breaks required.

The second visit was scheduled to take place within a month of the first visit to minimise changes associated with CA. On day two the family came to the CBCD,

where the eye-tracking tasks were carried out, which was identical to the TD procedure. Necessary breaks were provided if the participant expressed fatigue. The session lasted between 1 and 1.5 hours, depending on behaviour, technical issues and breaks required. During the session two saliva samples were collected to analyse DNA and RNA. At the end of the testing session the participant was provided with a certificate of participation, and travel costs were reimbursed.

2.4.3 Standardised assessments

All assessments described herein were attempted with all participants, although reduced abilities did prohibit inclusion of younger or less able participants in some more demanding tests. These tests are grouped together because they involve physical materials and experimenter-participant interaction. Although the majority of tests did provide standardised scores for interpretation, some did not.

Complication arises from applying tests standardised on the TD population to a special population such as those with DS. For example, with younger children with DS, and some older individuals with severe ID, there were problems with the administration of the standardised tests. This is because when individuals had very low verbal production or comprehension abilities, it was not feasible to follow the strict administration rules of certain tasks. In many cases, the prescribed method of administering the test was not adhered to, in order to maximise the data obtained from each session. It is possible that altering the application of the standardised tasks exaggerates the abilities of the individuals with DS, but without these slight alterations many individuals would have been at floor on all tasks. Therefore, the compromise of inflated abilities for more data on cognitive capabilities was deemed experimentally worthwhile.

In addition to this there are issues arising from the calculation of MA scores from raw scores in an atypical population. The raw scores are converted to MA equivalents based on typical population standardised scores for the CA of each participant. Applying this conversion to atypical individuals, such as those with DS, can risk contorting the results, as although there may be a range of raw scores achieved, once these are converted based on CA, the majority of individuals may be at or near floor. This reduces the potential inferences and analyses that the data are informative for by flattening the data range. Therefore, all MA measures of individuals with DS must be interpreted with caution, and supported by logic. Specifically in tasks where participants must score above a certain value to enable MA calculation, an issue arises in interpreting DS scores. Many individuals with DS score below the lowest raw score for their CA that permits MA conversion, meaning that although data has been collected, it cannot be interpreted. In these tasks it is preferable to use raw scores, as they are more informative about the range of abilities in the sample. Other tasks allow MA conversion from floor- a score of zero- for each CA, a method that permits inclusion of all individuals who attempted the task. These data can be used when calculated from the DS sample, but still should be interpreted with caution, as floor effects may actually inflate the perceived abilities of the DS group.

Tests are discussed in terms of their applicability to ranges of CA, the method of administration, and any methods used to avoid potential issues. The N that attempted each task and any MA equivalents produced are reported for each test individually, as well as a description of excluded individuals. The calculation of standardised scores and MA equivalents are not described herein, but details of these conversions are available in the manuals of each assessment.

2.4.3.1 British Picture Vocabulary Scale (BPVS-Third Edition)

The BPVS is a measure of receptive vocabulary for CA 3:00 to 16:11, developed to produce a standardised score, percentile rank and MA equivalent scores of receptive vocabulary (L. P. Dunn & Dunn, 2009; L. P. Dunn, Whetton, & Pintille, 1982). The BPVS administration lasted on average 15 minutes. It involved showing the participant a page with four images and asking, "which one is "…"?", or "show me "…"". One image is the correct answer, one image is a word phonologically close, one image is a picture within the same semantic category and one image is an unrelated distractor. Once the participant had made a selection the page was turned and the process was repeated with the next page until the ceiling level was reached, where eight or more errors are made in within a block of 12 pages.

Inclusion in this test required basic motor control and attention. Two participants with DS were unable to complete this task due to severe physical disabilities. The limitation of this test is that it was standardised on TD populations, and many children with DS achieved raw scores below the lowest TD percentile for their CA, meaning no percentile rank or age equivalent could be calculated. Where possible age equivalents were calculated, and for all participants "verbal scores" were calculated as described below.

VERBAL SCORE = Ceiling item achieved - Total errors made

This is a logical way of comparing atypical and typical individuals and enabled the inclusion of more individuals in the early childhood DS group, as shown in Table 2.4. This value captures the ability level of the individual, by their ceiling

score, but also appropriately represents their receptive vocabulary abilities up to the ceiling score. For example, in the DS group many individuals scored almost at ceiling in many blocks prior to actually reaching ceiling, whereas those in the TD group usually made very few errors until suddenly reaching their ceiling score. Therefore, the verbal score is representative of individuals' abilities without adjusting for CA. Calculating the verbal score no other participants were excluded beyond those with co-morbid disabilities.

Only six of the 22 individuals in the early childhood group with DS scored highly enough to calculate an MA. One participant of CA 5:07 scored highly enough to calculate an MA, the other 5 were CA 8:00 to 8:02. All other participants in this age-group did not score highly enough to calculate an MA. The participant with co-morbid ADHD did not complete the task. In contrast only one TD participant (CA 4:02) in the early childhood group did not score highly enough to calculate a MA. In late childhood only four participants with DS did not score highly enough to calculate a MA, including the participant with co-morbid ADHD. Standardised scores are not included, as they could only be calculated for five of the 43 participants with DS.

Table 2.4 MA equivalent and Verbal score means and ranges of DS and TD groups in each age-group

	Early Childhood		Late Childhood	
Measure	DS	TD	DS	TD
Original N	22	16	21	16
Verbal MA mean in months (range)	53.83 (45-59)	75.60 (52-104)	62.06 (52-93)	156.31 (99-192)
N (female)	6 (5)	15 (9)	16 (10)	16 (7)
Verbal Score mean (range)	39.95 (12-69)	88.34 (40-119)	66.15 (29-106)	143.69 (111-160)
N (female)	21 (12)	16 (10)	20 (11)	16 (7)

2.4.3.2 Components of the British Ability Scales (Second edition)

The following four tasks were taken from the British Ability Scale (second edition) (BAS 2), which is composed of a group of tasks that are combined to assess ability, and was developed for children CA 2:06 to 17:11 (Elliott, Murray, & Pearson, 1983). The four subscales included here (pattern construction, recall of digits forward, immediate and delayed verbal and visuospatial recall and recognition of pictures) were chosen because they were the only tasks that could be applied to children across the entire CA range included in the study. Administration of these tasks lasted approximately 30 minutes. One test is a core scale that measures non-verbal/spatial abilities; the other three tests are diagnostic subtests in the BAS 2 handbook, in that they are not used to calculate the General Composite Ability score associated with BAS 2 outcomes. The outcomes are raw socres, standard/ability scores, T-scores, percentiles and MA equivalents.

2.4.3.2.1 Pattern Construction

Pattern construction is a measure of non-verbal/spatial abilities. The MA equivalent outcome range in this test 3:06 to 14:11, although it was normed on CA 3:00 to 17:11 (Elliott, Murray, & Pearson, 1990). Non-verbal reasoning and visuospatial processing abilities were measured by reproducing designs with coloured blocks. The complexity of this task ranged from reproducing designs of two components, with a choice of 2 block types (black, yellow), to designs made of nine components with choice of 4 block types (black, yellow, diagonally half black/yellow, square half black/yellow). Depending on CA and ability, the start point was identified from the test booklet. If the participant was unable to complete the initial trials of each block, two demonstration trials were available at the start of each block. In the first section of the test the participant was provided with two blocks, yellow on one side and black on the other; they were shown a pattern of two black squares next to each other and instructed to "make the same pattern with your pieces". This section of the test had nine trials ranging from two to six squares. This lasted between 2 and 10 minutes. In the second section of the test the black/yellow blocks were replaced with 2D paper squares that were either all black, all yellow, diagonally divided into black and yellow triangles or divided into black and yellow oblongs. This section of the test had 18 trials, ranging from two to nine squares. This lasted between 5 and 15 minutes. The instructions are the same for all trials.

Inclusion in this task relied upon adequate motor control to pick up and manipulate the blocks involved. Inclusion in the second and harder part of the test relied upon the ability to manipulate the 2D square paper pieces. Many participants with DS completed the patterns directly on top of the presented pattern, as opposed

to on the table; this was always recorded and the results are included. The N of participants who attempted the task and their mean raw score achieved are shown in Table 2.5.

In the early childhood group four participants with DS were not included because they could not attempt this task due to limited motor abilities. All other participants were included. Adapted versions of the pattern construction material were used that in piloting, were found to be more appropriate to the participant group. While 3D cubes are used in the second section, instead 2D paper shapes were utilised. Participants were still required to complete the same target patterns from the shapes available. The identical version of the task was used with all participants in DS and TD groups. Given the altered materials caution was required in interpreting the performance on this task. Specifically, the 2D forms would likely inflate MA estimates. Therefore, out of caution, raw scores are used instead. To avoid floor effects in correlational analyses all individuals with a score of 0 were excluded, in the DS group 6 in early childhood and 1 in late childhood.

Initially the analyses were carried out with MA scores, but due to the concerns outlined above this was altered. It should be noted that the only difference this had on the results was a non-significant correlation between non-verbal raw scores and associative LTM, which was significant when correlated with MA in the DS group. This is a minor change in the outcomes overall, suggesting that both measures may have appropriately represented underlying cognitive abilities, despite the use of non-standard materials.

Table 2.5 Mean and range of non-verbal raw scores calculated from pattern construction, and N that produced data

	Early Childhood		Late Childhood	
Measure	DS	TD	DS	TD
Original N	22	16	21	16
Non-Verbal Mean raw score (range)	8.09 (1-19)	28.38 (6-51)	13.05 (1-25)	40 (19-62)
N (female)	11 (6)	16 (10)	19 (11)	16 (7)

2.4.3.2.2 Recall of digits forwards

Recall of digits forwards is a measure of auditory/verbal WM by oral recall of sequences of numbers ranging from two to nine digits long. The MA equivalent outcome range in this test is 4:00 to 13:11, although it was normed on CA 2:06 to 17:11 (Elliott et al., 1990). The experimenter recited the digits at a rate of two per second, the final digit at a lower pitch than the preceding digits. The participant was then asked to repeat the digits. The ceiling was reached when the participant recalled one or less item in a block of five items correctly. This lasted between 1 and 5 minutes. Inclusion in this task relied upon verbal ability, which excluded the majority of younger participants with DS, and some older, more severely disabled, participants with DS. The N of participants who attempted the task and their mean MA achieved are shown in Table 2.6.

In the early childhood group, 11 participants with DS were not included in calculating the digit MA because they were not capable of attempting this task, due to limited verbal abilities. In the late childhood group, 2 participants with DS were

not included due to not attempting the task, including the participant with co-morbid ADHD. All other participants were included. Again, no raw score was calculated for this measure because age equivalents can be produced from floor values. Therefore, all participants who attempted this task produced an MA, negating the need for raw score interpretations as in the BPVS.

Table 2.6 Mean and range of MA calculated from recall of digits forward, and N that produced data

	Early Childhood		Late Childhood	
Measure	DS	TD	DS	TD
Original N	22	16	21	16
Recall of Digit Mean MA in months (range)	53.60 (30-61)	90.19 (43-141)	61.11 (60-73)	162.75 (73-216)
N (female)	10 (7)	16 (10)	18 (11)	16 (7)

2.4.3.2.3 Immediate and delayed verbal and visuospatial recall

The immediate and delayed BAS 2 assessment is a measure of verbal and visuospatial WM and LTM. The MA equivalent outcome range in this test is 5:00 to 13:11, although it was normed on CA 4:00 to 17:11 (Elliott et al., 1990). A card of 4 x 5 images was displayed to the participant. The experimenter initially ensured each participant could name all the components. Depending on participants'

abilities, either the experimenter ran through the card twice more verbally naming the items with the participant, or the participant was left to memorise the items on the card unguided. All participants with DS were guided through the items twice more verbally before the initial test trial. The card was then turned over to obscure the images and the participant was prompted to verbally recall the components involved, “Now tell me as many of those pictures as you can. They don’t have to be in order”. Two more trials were completed in this manner, with the verbal instruction “Now tell me the same ones from before and some more”. In the second two trials the experimenter only guided the participants with DS through the images on the card once. The final component of the immediate recall involved providing 20 individual cards with the card components individually printed on, face-up before the participant and instructing them “These cards have the pictures on them, I want you to put them together so they look like the big picture you saw earlier. Try to remember where each picture should go”. The participants were also provided with a grid to obviate how the cards should be arranged, i.e. in a 4 x 5 grid. These immediate trials lasted approximately 10 minutes.

This task also had a “delayed” aspect, where after an interval of at least 15 minutes the participant was again presented with the back of the original card and asked, “Do you remember those pictures you saw? There were a lot on one card and you had to remember them. How many can you remember now? Tell me as many as you can”. There was also a repetition of the spatial aspect identical to the immediate test, but without any exposure to the pictures. The instructions were “Now I want you to try to remember where the pictures should go. Put these cards on the grid like you did before, to show where the pictures went”. With younger, or less able, participants the instructions were simplified to “make it look the same as before”,

or a comparable instruction set with simplified vocabulary. The delayed trials lasted approximately 5 minutes.

Inclusion in this task relied upon adequate verbal abilities to name the 20 images, and adequate motor control to pick up and manipulate the cards involved. All participants attempted the verbal task, but some who completed the verbal aspects could not complete the spatial tasks, due to the physical abilities required. Only those who completed the immediate memory tasks attempted the delayed memory tasks. The N of participants who attempted the task and their mean MA achieved are shown in Table 2.7.

In early childhood eight participants with DS were not included in the immediate verbal MA due to limited verbal abilities. One further participant was not included in the delayed verbal task analysis due to failure to engage in the task. In the spatial aspect 13 participants in early childhood with DS were not included in the immediate trial, due to failure to engage in the task, one further participant was excluded from the delayed trial only due to a failure to engage. In late childhood two participants with DS were excluded from both the immediate and delayed verbal trials due to an inability to engage with the task, including the participant with co-morbid ADHD. A further two participants were excluded from the immediate and delayed spatial tasks due to an inability to engage in the task. All other participants were included. Overall, more participants engaged in the verbal aspect of the task than the spatial. Again, no raw score was calculated for this measure because age equivalents can be produced from floor values.

Table 2.7 Mean and range of MA calculated from immediate verbal recall, and N that produced data for immediate and delayed verbal and spatial tasks

	Early Childhood		Late Childhood	
Measure	DS	TD	DS	TD
Original N	22	16	21	16
Immediate Verbal Mean MA in months (range)	56.85 (46-79)	83.86 (46-117)	65.94 (60-99)	159.94 (99-216)
Immediate Verbal N (female)	13 (8)	16 (10)	18 (11)	16 (8)
Immediate Spatial N (female)	8 (6)	16 (10)	16 (10)	16 (8)
Delayed Verbal N (female)	12 (8)	16 (10)	18 (10)	16 (8)
Delayed Spatial N (female)	8 (6)	16 (10)	16 (10)	16 (8)

2.4.3.2.4 Picture recognition

Recognition of pictures is a measure of short-term visual memory by recognition of images among distractors. The MA equivalent outcome range in this test is 4:06 to 7:05, although it was normed on 2:06 to 17:11 (Elliott et al., 1990). The target image was shown to the participants for five seconds, then the page was turned showing a collection of images including the target and distractor images and the participant was asked to identify the target image. The instructions in this task were, on the target image page: "look at this picture… let's find one like it on this page", then the page was turned and the experimenter said: "can you find it here?". From the first trial items onwards the instruction became "look at this/these", then the page was turned; "find it/them here". The ceiling was reached when five errors in six items were made. This task lasted between approximately 2 and 10 minutes.

Inclusion in this task relied upon ability to attend to the initial image and understand instructions. In some cases with younger participants with DS, and some older, more severely disabled, participants who failed the initial trial multiple times, they were allowed to name the item, this was always recorded and the results are included. The N of participants who attempted the task and their mean MA achieved are shown in Table 2.8.

In early childhood, two participants with DS were excluded from this analysis due to an inability to engage in the task. All other participants were included. Again, no raw score was calculated for this measure because age equivalents can be produced from floor values.

Table 2.8 Mean and range of non-verbal MA calculated from picture recognition, and N that produced data

	Early Childhood		Late Childhood	
Measure	DS	TD	DS	TD
Original N	22	16	21	16
Picture Recognition Mean MA in months (range)	39.53 (30-61)	86.00 (46-135)	63.70 (30-135)	175.94 (94-216)
N (female)	19 (12)	16 (10)	20 (11)	16 (7)

2.4.3.3 Rates of inclusion in standardised tasks

The percentage of each of the age-groups in both TD and DS groups that took part in each standardised task ranged across task, group and age-group, as shown in Figure 2.1. All TD participants were able to take part in all standardised tasks. In comparison, a higher percentage of the late childhood group were able to take part in all tasks than the early childhood group of participants with DS. Turning to the tasks, in general, more participants were able to take part in receptive language than expressive, and visuospatial processing than recall. The variability in those who engaged with each task was greater in early childhood than late childhood in the DS group, indicating that overall abilities improved with CA. In the early childhood group with DS, the completion rates of standardised tasks was very low, especially in the spatial memory tasks. This was caused by the level of fine motor skills required, and the instructions that needed to be understood. This is a commonly occurring issue of applying standardised tasks to an a typical population, and means that the interpretation of these results should be cautious, as the early

childhood group is not truly representative of the population. Unfortunately, this particular task required the manipulation of 20 small, 2D cards with pictures on it. The inclusion rate in this task could have been increased by reducing the size of the grid that was required to be recalled, and by providing the images on 3D blocks that are easier to manipulate. The low inclusion rates for the recall of digits task is in keeping with literature reported issues with this task. Comparing the inclusion rates for this task and the immediate verbal memory task of the BAS 2, the inclusion rates were almost 20% higher in the BAS 2 task. This highlights the specific difficulty in the DS population of engaging with number-based tasks, and also the benefit of assessing memory with more engaging, multi-format tasks, such as the BAS 2 where data is presented both visually and auditorily.

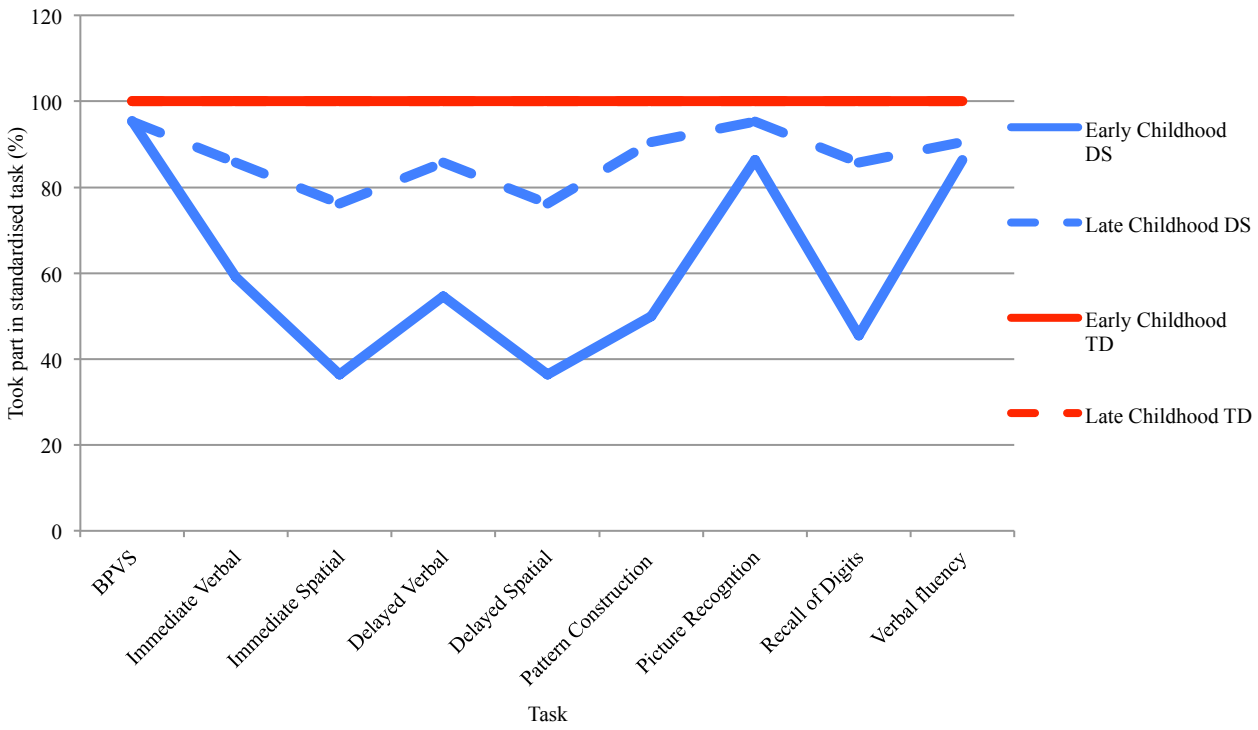

Figure 2.1 The percentages of each age-group within the two groups (DS and TD) that attempted each of the standardised tasks

2.4.4 Experimental assessments

Experimental assessments are non-standardised tasks; many were designed specifically for this study to investigate features of cognition in novel ways. The designs of these tasks are described, along with their outcomes for analysis, in the relevant chapters; the N of participants that successfully produced data for these tasks is shown in Table 2.9. Generalised methods for eye tracking studies (Chapter 3, Chapter 6, and Chapter 7) are outlined below.

2.4.4.1 Eye-tracking

For all eye-tracking tasks, participants sat in a dimly lit, featureless room, facing the stimulus-presentation screen with their eyes at a distance of approximately 65 cm from the screen. A Tobii Pro Tx300 remote eye tracker (Tobii Technology AB) was used to capture moment-to-moment point of gaze at a sampling rate of 120Hz, and a measurement accuracy of 0.5°. The experimenter sat behind a curtain and observed the participant using Tobii Studio LiveViewer via a camera that was positioned centrally and above the screen. The participants' eye movements were recorded using Tobii Studio 2.1.14. The visual stimuli were presented on a 34 x 27cm TFT liquid crystal display monitor, with a resolution of 1280 x 1024 pixels. The tracking equipment and stimulus presentation were controlled using either customised scripts in MATLAB R2013a or Tobii studio software. Auditory stimuli were delivered via two speakers positioned behind the display monitor and facing the participant. During all visual-only tasks, songs were played to increase engagement, and tests were interspersed with cartoon clips from "In the Night Garden" and "Waybuloo". All participants attempted this task, as there were no exclusion criteria, which is a major strength of this methodology. Some

participants produced less data due to ocular defects such as nystagmus or strabismus, which negatively impacted the Tobii's ability to track the gaze.

It should be noted that, due to a design error, it is unlikely that the object and object memory tasks measured memory accurately, this issue will be discussed in depth in the experimental chapter.

Table 2.9 N that produced data for experimental assessments

	Early Childhood		Late Childhood	
Task	DS (Female)	TD (Female)	DS (Female)	TD (Female)
Original N	22 (13)	16 (10)	21 (11)	16 (8)
Verbal fluency	19 (11)	16 (10)	19 (11)	16 (8)
Object memory	17 (10)	11 (7)	16 (9)	13 (7)
Object-in-place memory	15 (9)	13 (9)	16 (9)	13 (7)
Paired associate learning	18 (10)	13 (9)	17 (9)	13 (7)
Gap	14 (7)	15 (10)	16 (10)	15 (7)
Overlap	16 (8)	15 (10)	17 (10)	15 (7)
Baseline	18 (10)	15 (10)	15 (10)	15 (7)

2.4.4.2 Rates of inclusion in experimental tasks

The percentage of each of the age-groups in both TD and DS groups that took part in each experimental task ranged across task, group and age-group, as shown

in Figure 2.2. TD participants took part in more assessments than DS participants overall, although the difference was less obvious than in standardised tasks.

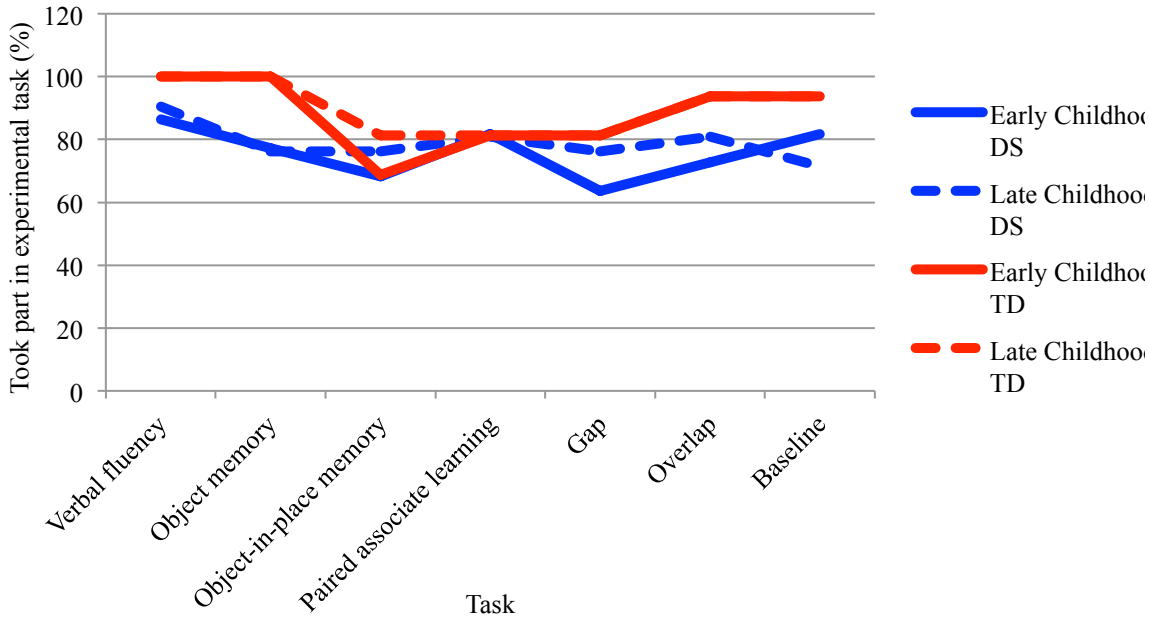

Figure 2.2 Percentage of each age-group within the two groups (DS and TD) that attempted each of the experimental tasks

2.4.4.3 Questionnaires

2.4.4.3.1 Paediatric sleep questionnaire (parent report) (Chervin, Hedger, Dillon, & Pituch, 2000)

This questionnaire was used to assess the presence of sleep-related breathing disorders, as these have been reported to be more common in the DS population than in TD individuals. In addition to this, sleep quality influences the development and ability level of many cognitive features, including memory, as will be discussed in the experimental Chapter 7. The PSQ consists of a series of 73 yes/no questions probing medical issues that may affect sleep behaviours, and six questions rated on a 4-point scale from "does not apply" to "definitely applies most of the time". This questionnaire was normed on CA between 2:00 and 18:00, and so

was used with all participants in this study. A subset of these questions (22) was used to calculate the risk in the child of sleep-related breathing disorders (SRBD). Internal consistency is sufficient (0.88), as is test-re-test reliability (.75). If the outcome is 0.33 or higher then the child is at risk of a SRBD (Chervin et al., 2000). The mean risk of SRBD in the DS group was 0.34, whereas the mean risk in the TD group was 0.15. The DS group were significantly more at risk of SRBD than the TD group ($t(62)=6.031$, $p<0.001$).

2.4.4.3.2 The Children's Behaviour Questionnaire (parent report)(Mary K Rothbart, Ahadi, Hershey, & Fisher, 2001)

This questionnaire was used to assess behavioural features of the early childhood group. Some measures, such as impulsivity and inhibitory control, have previously been correlated with cognitive abilities, these will be presented in the experimental chapter. The CBQ consists of 195 questions answered on a Likert scale from 1 to 7, from "extremely untrue" to "extremely true". This questionnaire was normed on children aged 3:00 to 7:11 (Mary K Rothbart et al., 2001). Internal validity is sufficient (0.51), as is test-retest reliability (0.63). After corresponding with the authors about the targeted age range, it was decided that it would be most appropriate to send this to the parents of all participants in the early childhood group. These raw scores are formulaically converted to scales presented in Table 2.10.

Table 2.10 The Children's Behaviour Questionnaire scales and their definitions

Scale (Questions in scale)	Definition
Activity Level (13)	Level of gross motor activity including rate and extent of locomotion.
Anger/Frustration (13)	Amount of negative affect related to interruption of on-going tasks or goal blocking.
Approach (13)	Amount of excitement and positive anticipation for expected pleasurable activities.
Attentional Focusing (14)	Tendency to maintain attentional focus upon task-related channels.
Discomfort (12)	Amount of negative affect related to sensory qualities of stimulation, including intensity, rate or complexity of light, movement, sound, texture.
Falling Reactivity and Soothability (13)	Rate of recovery from peak distress, excitement, or general arousal.
Fear (12)	Amount of negative affect, including unease, worry or nervousness related to anticipated pain or distress and/or potentially threatening situations.
High Intensity Pleasure (13)	Amount of pleasure or enjoyment related to situations involving high stimulus intensity, rate, complexity, novelty and incongruity.
Impulsivity (13)	Speed of response initiation.

Inhibitory Control (13)	The capacity to plan and to suppress inappropriate approach responses under instructions or in novel or uncertain situations.
Low Intensity Pleasure (13)	Amount of pleasure or enjoyment related to situations involving low stimulus intensity, rate, complexity, novelty and incongruity.
Perceptual Sensitivity (12)	Amount of detection of slight, low intensity stimuli from the external environment.
Sadness (12)	Amount of negative affect and lowered mood and energy related to exposure to suffering, disappointment and object loss.
Shyness (13)	Slow or inhibited approach in situations involving novelty or uncertainty.
Smiling and Laughter (13)	Amount of positive affect in response to changes in stimulus intensity, rate, complexity, and incongruity.

2.4.4.3.3 The Early Adolescent Temperament Questionnaire (parent report) (L. K. Ellis & Rothbart, 2001)

This questionnaire was used to capture behavioural features of the late childhood group, comparable to those captured by the CBQ. These features are also correlated with cognitive outcomes in the experimental chapter. The EATQ consists of 62 questions answered on a Likert scale from 1 to 5, from "almost always untrue" to "almost always true". These scores are formulaically converted into the scales presented in Table 2.11. These scales are converted into four "super scales": Effortful Control, Surgency, Negative Affect, and Affiliativeness. This questionnaire

was normed on individuals aged 10:00 to 16:11 (L. K. Ellis & Rothbart, 2001). Internal validity is sufficient (0.29), as is test-retest reliability (0.50). After corresponding with the authors about the targeted age range, it was decided that it would be most appropriate to send this to the parents of all participants in the late childhood group.

Table 2.11 The Early Adolescent Temperament Questionnaire scales, super scales, and their definitions

Temperament Scales (questions in scale)	
Activation Control (7)	The capacity to perform an action when there is a strong tendency to avoid it.
Affiliation (6)	The desire for warmth and closeness with others, independent of shyness or extraversion.
Attention (6)	The capacity to focus attention as well as to shift attention when desired.
Fear (6)	Unpleasant affect related to anticipation of distress.
Frustration (6)	Negative affect related to interruption of on-going tasks or goal blocking.
High Intensity Pleasure/Surgency (9)	The pleasure derived from activities involving high intensity or novelty.
Inhibitory Control (5)	The capacity to plan, and to suppress inappropriate responses.

Shyness (5)	Behavioural inhibition to novelty and challenge, especially social.
Behavioural Scales	
Aggression (7)	Hostile and aggressive actions, including person- and object-directed physical violence, direct and indirect verbal aggression, and hostile reactivity.
Depressive Mood (5)	Unpleasant affect and lowered mood, loss of enjoyment and interest in activities.
Super Scales	
Effortful Control	Attention, Inhibitory Control, Activation Control
Surgency	Surgency, Fear (reverse scored), Shyness (reverse scored)
Negative Affect	Frustration, Depressive Mood, Aggression
Affiliativeness	Affiliation

2.4.4.3.4 The Vineland Questionnaire (parent report) (S. S. Sparrow, Cicchetti, & Balla, 1989)

The Vineland measures adaptive behaviour, and was used as it can be applied across the full range of CA used herein. The adaptive behavioural composite score derived from a combination of all the domins, was correlated with associative memory abilities, as these have previously been associated in the literature, as will be discussed in the experimental chapter. The Vineland consists of four major domains: Communication, Daily Living Skills, Socialisation, and Motor Skills. These domains are made up of three subdomains, except motor skills, which is made up of two subdomains. The subdomains are presented in Table 2.12. The four domains

also convert into an adaptive behaviour composite (ABC) score. Each domain and the ABC have both percentile rank and adaptive level outcomes. Each subdomain has an MA equivalent score, which can be informative in assessing strengths and weaknesses in children with DS. This was normed on individuals from birth to 90:00 (Community-University Partnership for the Study of Children, Youth, and Families, 2011). Internal validity is sufficient (0.93), as is test-retest reliability (0.76) (Community-University Partnership for the Study of Children, Youth, and Families, 2011). This was sent to the parents of all participants.

Table 2.12 The Vineland domains, subdomains and questions in each subdomain

Domain	Subdomains (questions in subscale)
Communication	Receptive (20)
	Expressive (54)
	Written (25)
Daily Living Skills	Personal (41)
	Domestic (24)
	Community (44)
Socialisation	Interpersonal Relationships (38)
	Play and Leisure Time (31)
	Coping skills (30)
Motor Skills	Gross Motor (40)
	Fine Motor (36)

2.4.5 Coding and analyses

Various software programmes were used to code, extract, analyse and manipulate the data. The standardised scales were coded and analysed using manuals and Microsoft Excel. Eye-tracking data were analysed using both MATLAB (MathWorks, 2012) and Excel formatted sheets. Statistical analyses were carried out with IBM SPSS Statistics, Version 20 (IBM, 2011). The majority of analyses are ANOVA or ANCOVA, although some t-test and correlation analyses are also

included. If the results are reported then the assumptions of these tests were satisfied. No correction for data distribution was carried out, parametric analyses can be carried out on non-normal data in certain circumstances, for example, when each group had an N of at least 15, and if Levene's variance or Box's were non-significant. In general, no outlier was excluded unless there was a malfunction during data collection, or a note that the participant did not engage in the trial. This was to ensure studies characterized the range of performance in the population. If a participant had missing data they were excluded from the analysis- no imputation was carried out. In the Trajectories chapter, data points that had undue influence on gradients or intercepts were excluded per Cook's distance, as these outliers would render the trajectories non-representative of the CA-performance or MA-performance relationship.

2.4.5.1 Analyses of standardised assessments

In order to investigate verbal and non-verbal cognitive abilities, standardised tests that produce MA equivalents for verbal and non-verbal abilities were carried out. This allows control for MA in future correlation analyses. In typical development, there should be a high correlation between CA and MA. However, in atypical development the relationship is not necessarily linear, as cognitive skills assessed by these tasks may not develop synchronously. Before moving on to the experimental chapters it is necessary to characterise the results of the standardised tests described, including the measures of verbal and non-verbal cognition. This is to illustrate the potentially uneven cognitive profile of development in the DS population over development. In addition to this, many standardised test results are used as covariates and correlates in experimental

chapters, therefore it is desirable to characterise these results before these analyses.

An overall representation of the mean CA, MA and other scores are represented in Table 2.13. It should be noted that the verbal MA of the DS group is inflated by failing to take into consideration individuals below the threshold where MA could be calculated. All other tasks included individuals at floor and thus do not inflate the scores in the DS group. Group by age group comparisons are included, along with plots of abilities over age to illustrate the development of abilities between groups.

Table 2.13 A comparison of CA and cogntive measures calculated from previously described standardised tests within early and late childhood groups

	Early Childhood				Late Childhood			
	DS	TD	*p*	η_p^2	DS	TD	*p*	η_p^2
CA	73.55	71.19	0.718	0.004	147.95	139.63	0.246	0.040
BPVS MA months [range]	53.83 [45-64]	75.60 [52-171]	<0.001	0.532	62.06 [52-93]	156.31 [99-192]	<0.001	0.777
Verbal score [Range]	38.80 [12-79]	88.38 [40-149]	<0.001	0.614	66.15 [29-106]	143.69 [111-160]	<0.001	0.861
Pattern Construction Raw Score	8.09 [2-19]	28.38 [6-51]	<0.001	0.423	13.05 [1-25]	40.00 [19-63]	<0.001	0.624

[Range]							
Immediate Verbal MA in months [Range]	56.85 [46-79]	83.88 [46-213]	<0.001	0.383	65.94 [60-99]	159.94 [99-216]	<0.001	0.720
Picture Recognition MA in months [Range]	39.53 [30-61]	86.00 [46-195]	<0.001	0.643	63.70 [30-135]	175.94 [94-216]	<0.001	0.752
Digit MA in months [Range]	3.60 [30-61]	90.19 [43-216]	<0.001	0.496	61.11 [60-82]	162.75 [73-216]	<0.001	0.651

2.4.5.1.1 The British Picture Vocabulary Scale

Two measures were derived from the BPVS: MA equivalents and the verbal score. The MA was more strongly correlated with CA in the TD, $r(35)=0.901$, $p<0.001$, than in the DS group, $r(39)=0.765$, $p<0.001$, as shown in Figure 2.3. The verbal score was more strongly correlated with CA in the TD, $r(33)=0.847$, $p<0.001$, than in the DS group, $r(21)=0.533$, $p=0.011$, as shown in Figure 4.4. Overall, although the MA scores were strongly correlated with CA, the verbal score explained more of the variance in the DS group over CA, showing this measure was more informative. For this reason the verbal score will be used in future analyses as a verbal measure, rather than the BPVS MA. This is an example of how controlling for CA in a standardised task in an atypical population can alter the relationship perceived between typical and atypical groups.

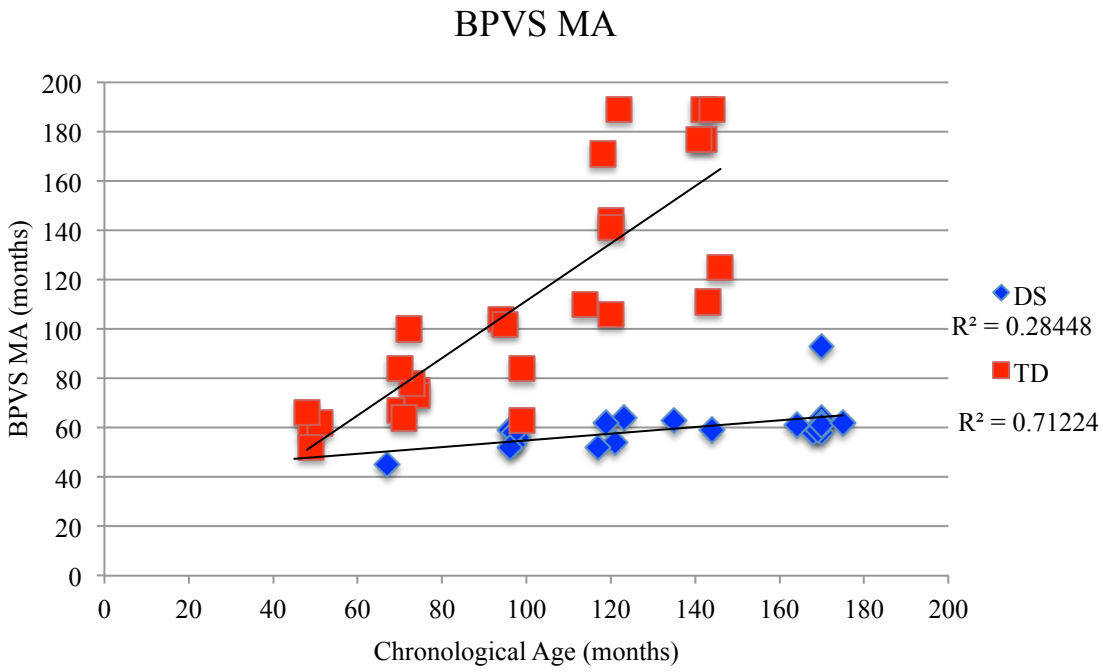

Figure 2.3 The relationship between CA and BPVS MA

As can be seen in Figure 2.4, although the TD group overall scored higher, there were overlapping participant scores. Interestingly, when looking at the MA data, although the two groups have comparable start points, they rapidly diverge across development. This is a visual representation of what happens when a standardisation technique normed on the typical population is applied to an atypical population.

A two-way ANOVA was conducted that examined the effect of age and group on the verbal score data, the DS group scored significantly lower than the TD group ($F(1,69)=225.36$, $p<0.001$, $\eta_p^2=0.766$). The early childhood group scored significantly lower than the late childhood group ($F(1,69)=94.37$, $p<0.001$, $\eta_p^2=0.578$). The relationship between early and late childhood groups in DS and TD groups were significantly different ($F(1,69)=12.04$, $p=0.001$, $\eta_p^2=0.149$), indicating the trajectories of development are significantly different even in this more moderate measure of verbal development.

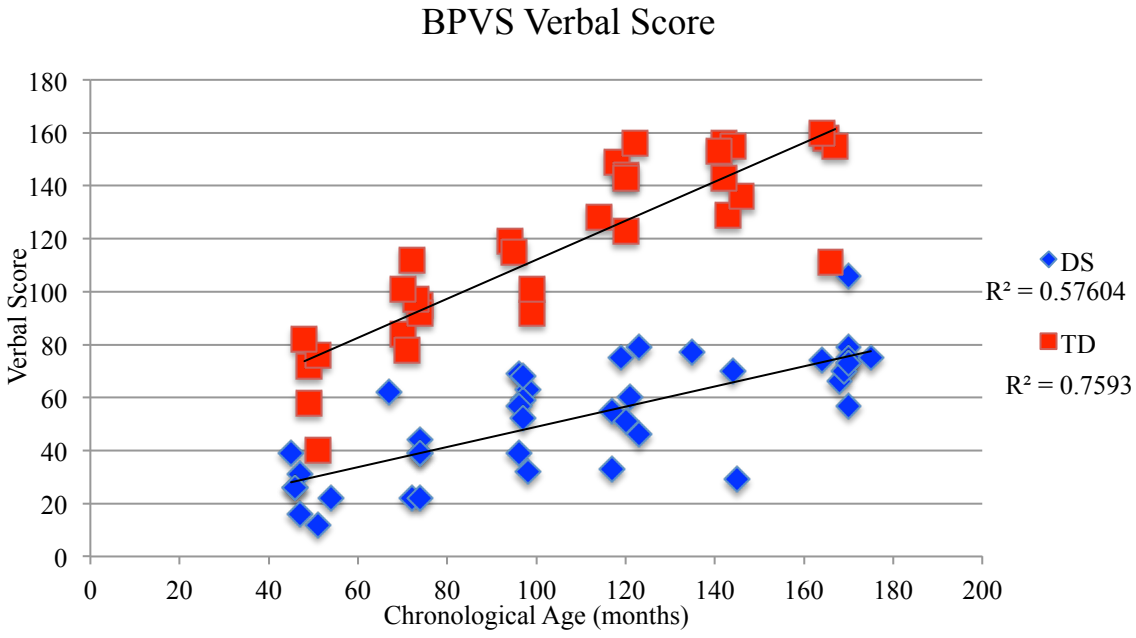

Figure 2.4 The relationship between CA and verbal score

2.4.5.1.2 Pattern construction

The raw pattern construction score explained more variance in the TD group across CA, $r(35)=0.599$, $p<0.001$, than in the DS group, $r(30)=0.308$, $p=0.097$, as shown in Figure 2.5. A two-way ANOVA was conducted that examined the effect of age and group on non-verbal raw scores, the DS group scored significantly lower than the TD group ($F(1,58)=64.64$, $p<0.001$, $\eta_p^2=0.527$). The early childhood group scored significantly lower than the late childhood group ($F(1,58)=7.97$, $p=0.006$, $\eta_p^2=0.121$). The relationship between raw scores in early and late childhood in DS and TD groups were not significantly different ($F(1,58)=1.29$, $p=0.261$, $\eta_p^2=0.022$), indicating the trajectories of development were not significantly different.

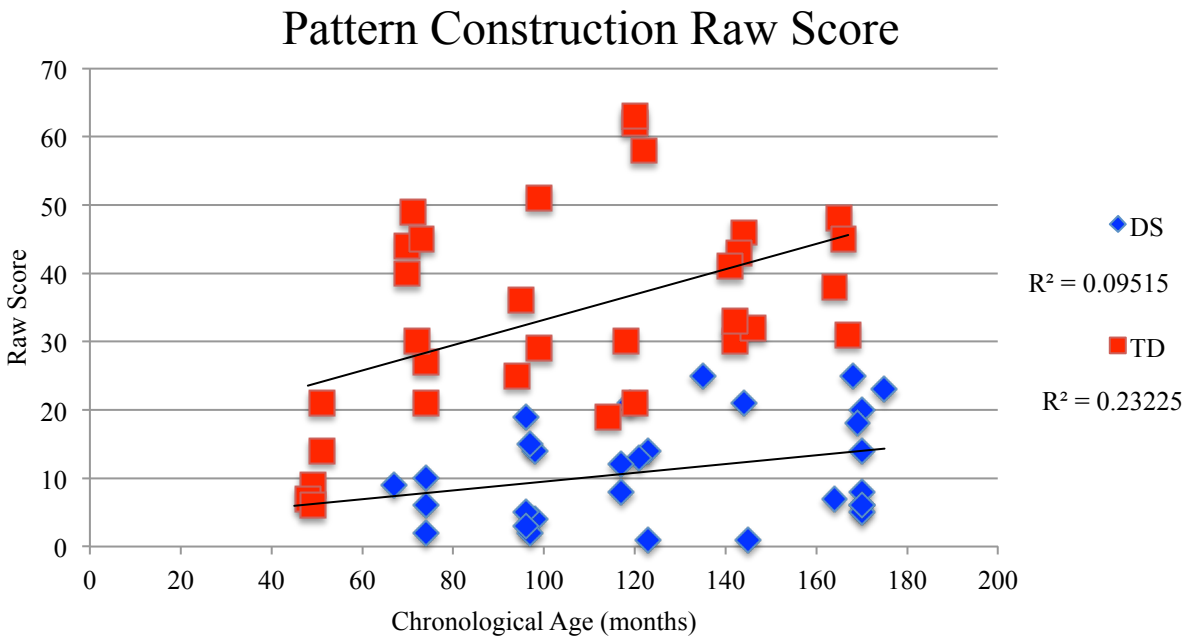

Figure 2.5 The relationship between CA and pattern construction raw scores

To establish the implication of using pattern construction raw scores rather than MA equivalents, the relationship between MA and CA was also investigated and is presented in Figure 2.6. As is clear from the graph and the equations, converting to MA reduces the variability of outcomes in the DS population. It is desirable to use data that are more sensitive to the range of abilities in the DS population, as is seen in the raw score data. Therefore, the use of this raw score measure is preferable.

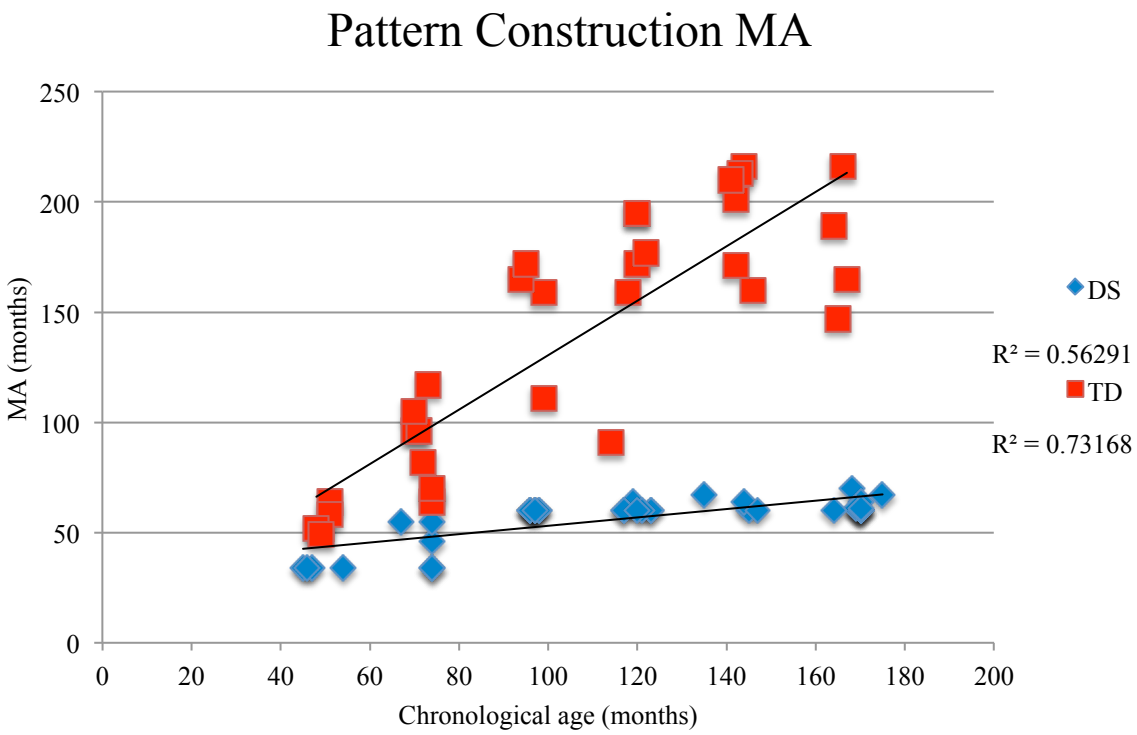

Figure 2.6 The relationship between CA and pattern construction MA

2.4.5.1.3 Recall of digits

Many of the younger participants with DS were unable to attempt recall of digits forwards. The relationship between CA and digit recall raw scores was significant in the TD group, $r(35)=0.721$, $p<0.001$, whereas in the DS group the

relationship was non-significant, $r(27)=0.201$, $p=0.305$, as shown in Figure 2.7. A two-way ANOVA was conducted that examined the effect of age and group on digit recall raw scores, the DS group scored significantly lower than the TD group ($F(1,56)=175.32$, $p<0.001$, $\eta_p^2=0.758$). The early childhood group scored significantly lower than the late childhood group ($F(1,56)=9.91$, $p<0.001$, $\eta_p^2=0.150$). The relationship between early and late childhood groups in DS and TD groups were not significantly different ($F(1,56)=2.65$, $p=0.109$, $\eta_p^2=0.045$), indicating the trajectories of development of raw scores were not significantly different.

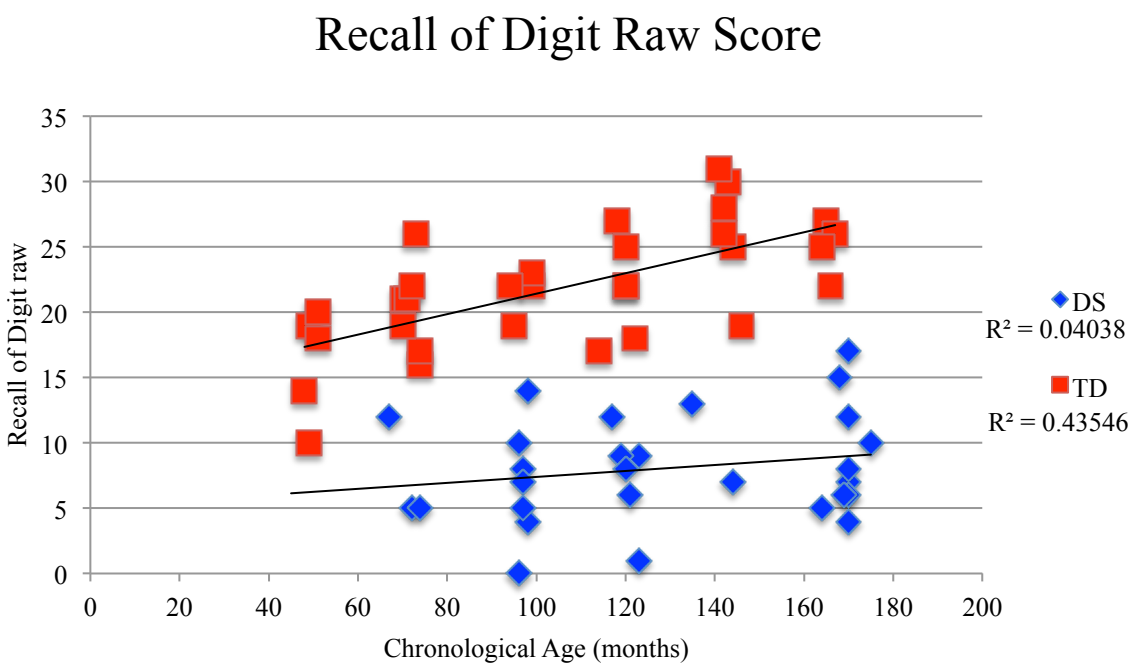

Figure 2.7 The relationship between CA and recall of digit raw scores

The relationship between CA and digit recall MA equivalents explained more variance in the TD, $r(35)=0.797$, $p<0.001$, than in the DS group, $r(27)=0.534$, $p=0.003$, as shown in Figure 2.8. A two-way ANOVA was conducted that examined the effect of age and group on digit recall MA, the DS group scored significantly

lower than the TD group ($F(1,56)=72.06$, $p<0.001$, $\eta_p^2=0.563$). The early childhood group scored significantly lower than the late childhood group ($F(1,56)=24.18$, $p<0.001$, $\eta_p^2=0.302$). The relationship between early and late childhood groups in DS and TD groups were significantly different ($F(1,56)=15.96$, $p<0.001$, $\eta_p^2=0.222$), indicating the trajectories of development of MA were significantly different.

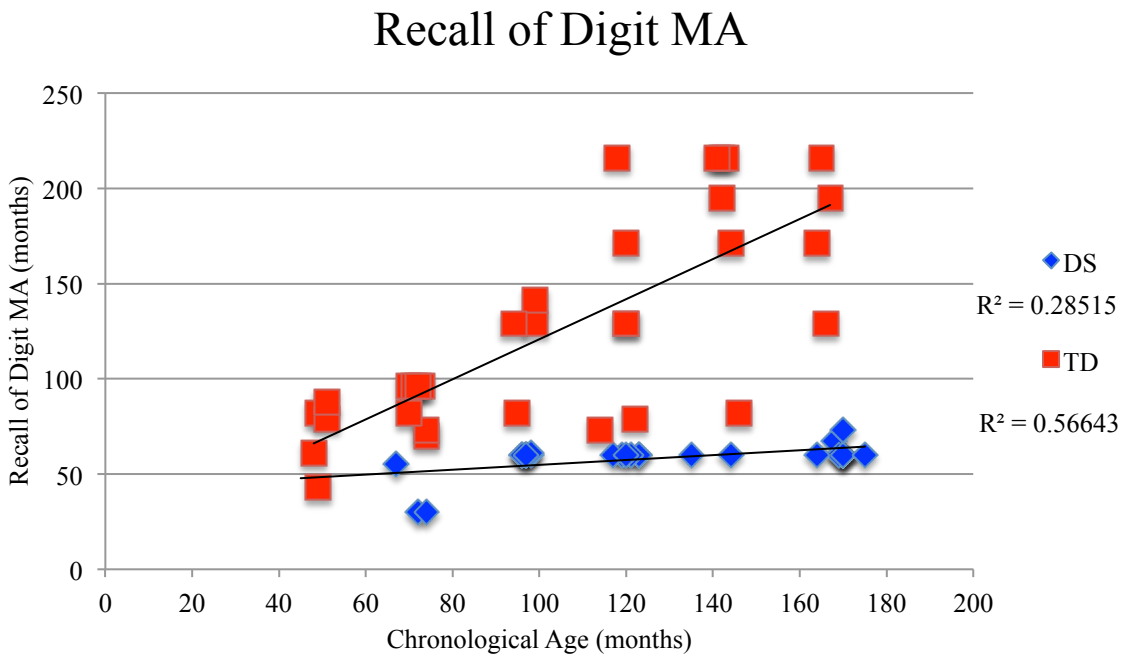

Figure 2.8 The relationship between CA and recall of digits MA

2.4.5.1.4 Immediate verbal memory

Immediate verbal memory is the assessment out of these four assessments that the most participants successfully partook in; this sub-test also provided an MA equivalent. Similarly to the BPVS and pattern construction MA equivalents, at younger CA the scores appeared more similar, but with increasing age the trajectory diverged further from each other, as shown in Figure 2.9. CA explained

more of the variance in immediate verbal MA in the TD group, $r(35)=0.833$, $p<0.001$, than in the DS group, $r(30)=0.580$, $p=0.001$. A two-way ANOVA was conducted to investigate the effect of age and group on digit recall MA, the DS group scored significantly lower than the TD group ($F(1,59)=93.33$, $p<0.001$, $\eta_p^2=0.613$). The early childhood group scored significantly lower than the late childhood group ($F(1,59)=46.22$, $p<0.001$, $\eta_p^2=0.439$). The relationship between early and late childhood groups in DS and TD groups were significantly different ($F(1,59)=28.58$, $p<0.001$, $\eta_p^2=0.326$), indicating the trajectories of development of verbal MA were significantly different.

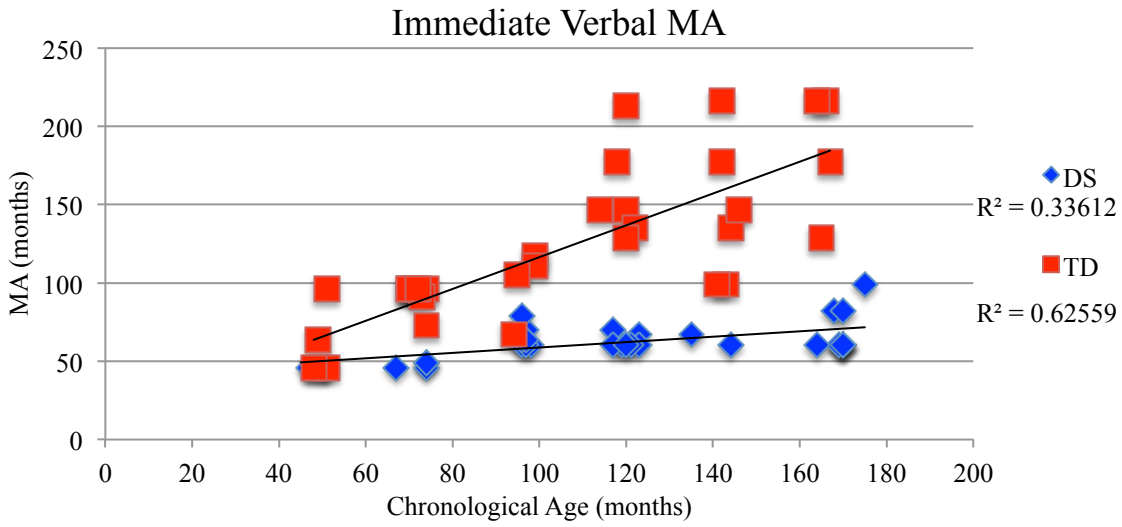

Figure 2.9 The relationship between CA and immediate verbal recall MA

2.4.5.1.5 Picture recognition

The majority of participants were able to engage with the picture recognition task. CA explained more of the variance in picture recognition raw scores in the TD group, $r(35)=0.620$, $p<0.001$, than the DS group, $r(38)=0.510$, $p<0.001$, as shown in Figure 2.10. A two-way ANOVA was conducted to examine the effect of age and group on picture recognition raw score, the DS group scored

significantly lower than the TD group ($F(1,67)=76.72$, $p<0.001$, $\eta_p^2=0.503$). The early childhood group scored significantly lower than the late childhood group ($F(1,67)=29.97$, $p<0.001$, $\eta_p^2=0.309$). The relationship between early and late childhood groups in DS and TD groups were not significantly different ($F(1,67)=0.884$, $p=0.35$, $\eta_p^2=0.013$), indicating the trajectories of development of raw scores were not significantly different.

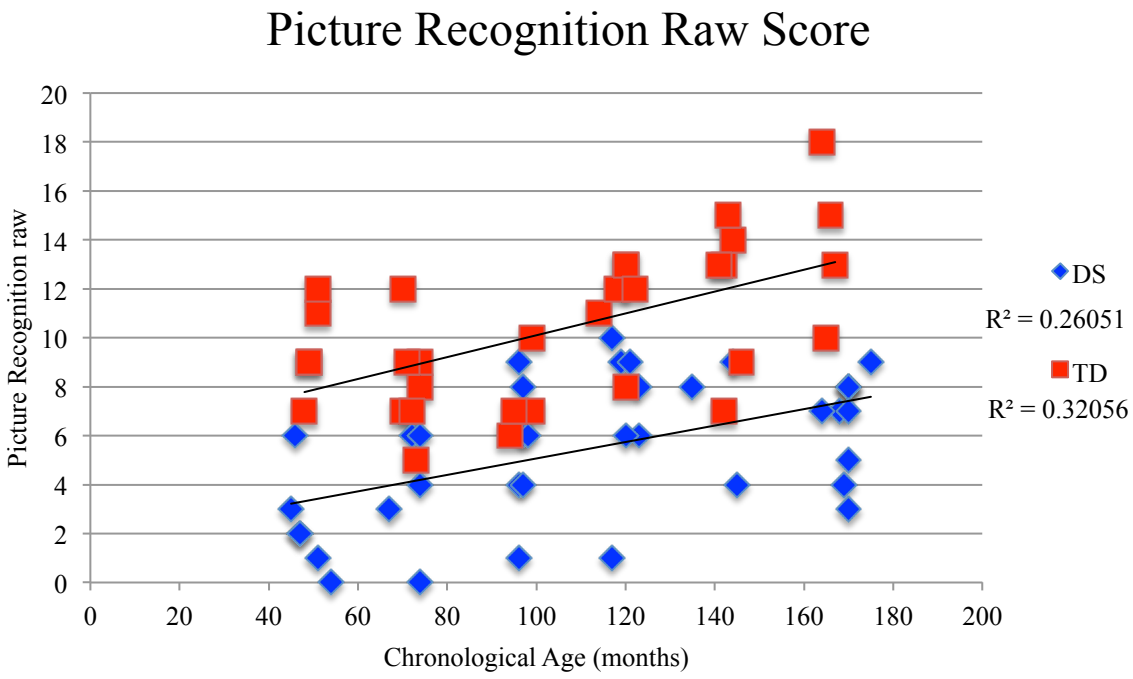

Figure 2.10 The relationship between CA and picture recognition raw scores

CA also explained more of the variance in picture recognition MA in the TD group, $r(35)=0.856$, $p<0.001$, than the DS group, $r(38)=0.658$, $p<0.001$, as shown in Figure 2.11. A two-way ANOVA was conducted to examine the effect of age and group on picture recognition MA, the DS group scored significantly lower than the TD group ($F(1,67)=176.67$, $p<0.001$, $\eta_p^2=0.724$). The early childhood group scored significantly lower than the late childhood group ($F(1,67)=90.81$, $p<0.001$,

η_p^2=0.575). The relationship between early and late childhood groups in DS and TD groups were significantly different (F(1,67)=30.16, p<0.001, η_p^2=0.310), indicating the trajectories of development of visual MA were significantly different.

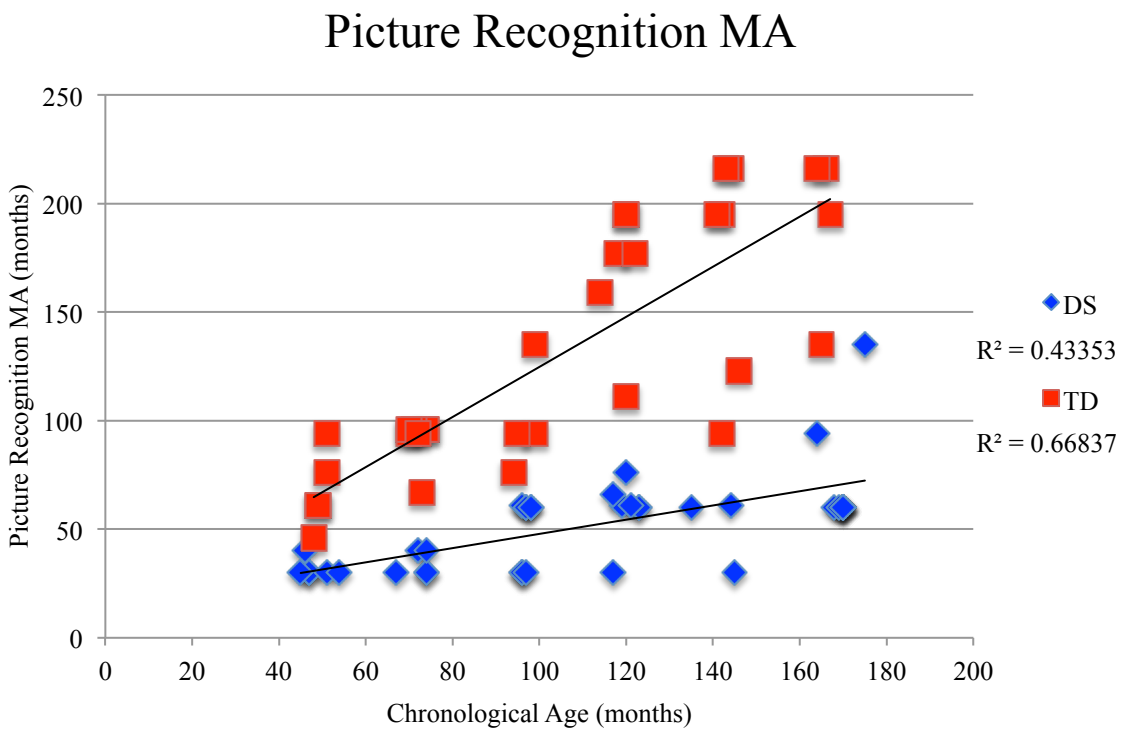

Figure 2.11 The relationship between CA and picture recognition MA

2.4.5.2 Summary

The participants' recruitment, testing protocol and demographic backgrounds were characterised. The tasks used in this research project have been described with inclusion criteria and the appropriate ages of assessment. The outcome measures of each task, with mean MA and N that successfully participated in each task were outlined. The methods used for analysis were also described. Each of the standardised task raw and MA equivalent outcomes were correlated with CA in each experimental group. The relationships between the groups over age were reported for each standardised task. The groups were split into early and late

childhood to analyse change in cognitive abilities over development. We now move on to the experimental studies.

Chapter 3 Visual and Visuospatial Short-Term Memory

3.1 Introduction

In this section the relevant theories of memory are outlined. Visuospatial memory-related findings in the TD and DS populations in terms of these theories are then reviewed. The contribution to this field of the mouse literature, which was heavily influential on the design of the paradigms used herein, is then described, before discussing the current study. As the current study uses a novel paradigm, there is limited literature studying the DS population that is relevant, therefore only a brief outline of the results to date that informed the hypotheses will be covered.

3.1.1 Theories of visuospatial memory

Visuospatial memory is memory for orientation and surroundings, allowing an individual to navigate a novel environment and identify changes in visual details. Visuospatial WM is theorised to rely on the visuospatial sketchpad, which stores and processes information in a visual form (Logie, Venneri, Sala, Redpath, & Marshall, 2003). There are two temporal sub-divisions of visuospatial memory: sequential and simultaneous, depending on the stimulus presentation form (Frick, 1985; Pazzaglia, 1999).

Visuospatial memory can be separated into both visual and spatial aspects. Visual, or object, memory is the specific ability to recall an object alone, not in relation to the environment but as a unitary construct, the "what" of memory. This is processed via the visual cortex and ventral visual stream, before reaching the limbic system (Jarrold, Nadel, & Vicari, 2008). Spatial, or location, memory is memory of the layout of the scene- its spatial orientation. This does not require memory of the details of specific units within the scene, only their relationship to

each other, the "where" of memory. This is processed via the visual cortex and the dorsal visual stream to the limbic system (Jarrold et al., 2008), see Figure 3.1.

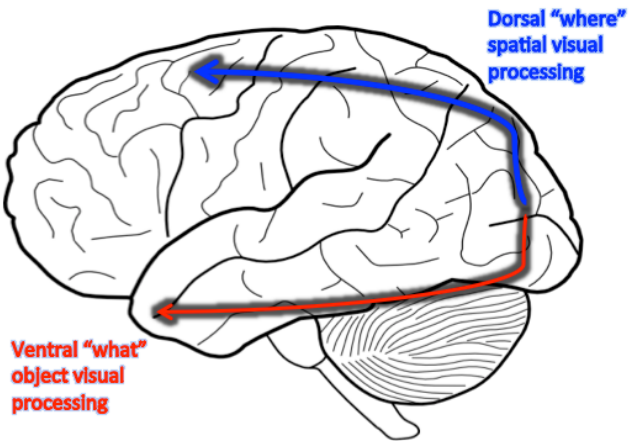

Figure 3.1 The separate processing pathways of visual and spatial memory from the visual cortex towards the PFC, adapted from (Goodale & Milner, 1992)

Functional studies show object processing preferentially activates the amygdala, spatial processing activates the hippocampus, and pattern processing activates both the amygdala and entorhinal cortex, with minimal hippocampal activation, illustrating the different structural components involved in processing information, even within memory formats (Kreiman, Koch, & Fried, 2000). A combination of visual and spatial memory, visuospatial memory, is referred to in this chapter as "object-in-place" memory. Therefore, there are three types of visuospatial memory: purely visual, purely spatial, and visuospatial.

This theoretical division of abilities was supported by findings in patients who had suffered brain injuries, impairing specific memory functions, i.e., visual or spatial (Farah, Hammond, Levine, & Calvanio, 1988; Luzzatti, Vecchi, Agazzi, Cesa-Bianchi, & Vergani, 1998). For example, injury to the right parietal lobe causes spatial processing defects, whereas injury to the right temporal lobe causes visual

closure errors (F. Newcombe, Ratcliff, & Damasio, 1987). These visual and spatial systems are separable but also linked, as evidenced by the fact that visual interference disrupts visual tasks more strongly, and spatial interference disrupts spatial tasks more strongly, but both forms of interference affect both memory systems to some degree (Della Sala, Gray, Baddeley, Allamano, & Wilson, 1999; Hecker & Mapperson, 1997; Klauer & Zhao, 2004).

Sequential visuospatial WM is typically tested using presentation of sequence of movements in space, such as the Corsi block test (L. Jaap Kappelle, 2000). Simultaneous visuospatial WM is typically tested using presentation of a matrix of black and white squares, which the participants are requested to reconstruct from a purely white matrix (Lanfranchi, Carretti, et al., 2009). Sequential and simultaneous memories are also referred to in the literature as dynamic and static memory, respectively (Pickering, Gathercole, Hall, & Lloyd, 2001). There is some room for confusion here, as static presentation of spatial stimuli can also be considered a visual task and dynamic presentation of visual stimuli can be considered a spatial task. Therefore, the degree to which visual and spatial aspects of memory can be separately assessed is questionable and should be clearly critiqued within each study. Perhaps the best way of ascertaining what memory systems are being utilised would be through applying different interference methods and observing which method most disrupts abilities.

Another important, and compatible, theory of memory is that of Cornoldi and Vecchi, who theorised that memory is arranged on two axes (Cornoldi & Vecchi, 2004). The horizontal axis is the format of presentation or encoding of the stimuli, i.e. verbal, visual, or spatial. The vertical axis of memory is the level of cognitive or executive control required to maintain or encode the stimuli information, i.e. low

control remembering where your house is, high control retracing a route you have only taken once, after a period of delay. This theory benefits us by allowing the consideration of cognitive development in terms of memory format and task difficulty, rather than reducing the discussion to merely visual or spatial processing abilities.

3.1.2 Visuospatial memory in typical development

Anatomically the two systems of visual and spatial memory processing originate in the visual cortex and terminate in the prefrontal cortex (PFC), but are processed via different pathways (Courtney, Ungerleider, Keil, & Haxby, 1996; Goodale & Milner, 1992; Haxby et al., 1991). Many real-world tasks require the combined actions of both visual and spatial memory processing abilities. For example, to remember the item you are looking for (visual), and the location it was left in (spatial).

In addition to ascertaining which memory subsystem is being used, there is also the presentation of the stimuli, and method of testing, to consider. This is comparable to the horizontal axes of Cornoldi and Vecchi's theory of memory, the mode of presentation of the stimuli. Although the focus of this chapter is visuospatial memory, data can be presented to the participants in a range of formats, which may alter the efficiency of the memory storage and retrieval. For example, visual stimuli can be presented alone (picture of a cow), or with verbal labels (picture and word "cow"), or associated audio data (picture and sound "moo"). For example, on hearing the words "your shoes are in the kitchen", an image of an item in a location can be visualised to increase the richness of the memory, or to recode the verbal information into a visuospatial format. Similarly, when giving or receiving directions memory recall can benefit from cognitive visual

enacting of the routes being discussed (De Beni, Pazzaglia, Gyselinck, & Meneghetti, 2005).

There is some evidence that over development the preferential format of memory encoding changes. Before CA 4 years, there is no preference; from aged 4 to 7 years TD individuals preferentially encode memory visuospatially; from aged 7 years verbal memory is the preferential form of encoding (Palmer, 2000). Therefore, the stimuli presentation format may affect the success of memory encoding depending on the developmental stage of the individual. In addition to stimulus presentation variation, there is also potential variability in the method of assessment. For example, participants may be required to recall a visual feature or spatial layout, or recognise the original stimulus among a number of distractors. Recall is thought to demand more cognitive control than recognition. Therefore, when assessing visuospatial memory, the mode of stimuli presentation and memory testing, and the CA of the group, has the potential to alter the perceived ability level of the participants.

As the focus of this chapter is simultaneous memory assessments, sequential visuospatial memory abilities will not be discussed in detail. Investigations into static and dynamic memory, which are analogous to simultaneous and sequential stimulus presentations, showed that between the ages of 5, 8 and 10 years, simultaneous memory was constantly better than sequential (Pickering et al., 2001). The same study showed that from age 6 to 10 years simultaneous memory developed more than sequential memory, articulatory and spatial suppression equally impaired simultaneous memory at aged 6, but not aged 10, and had no effect on sequential memory at either age (Pickering et al., 2001). Thus, simultaneous memory constantly out-performs sequential, but is also more

vulnerable to interference from both verbal and visuospatial distractors. However, at aged 10 years articulatory suppression actually increased overall simultaneous visuospatial memory ability (Pickering et al., 2001). Therefore, older individuals benefit from articulatory suppression when carrying out simultaneous visuospatial recall tasks. The finding that sequential memory is not affected by either form of interference suggests the mechanisms involved are relatively simple and do not require maintenance, preventing any effects of interference.

Visual simultaneous recognition memory for patterns improved from aged 5 to 11 years, at which point it is thought to have reached adult levels and thus plateaus from 11 years onwards (Wilson, Scott, & Power, 1987). Visuospatial STM and WM improve from age 4 to 11 years overall, tested by dot matrix, maze memory, Corsi block recall and odd-one-out recall (Alloway et al., 2006; Gathercole, 1998). In visuospatial memory, there is a similarity phenomenon called the visual similarity effect (VSE). This is observed in some, but not all, children aged 3 years (Palmer, 2000). The VSE is also observed at ages 5, 6 and 7 years, and in adulthood (Hitch, Woodin, et al., 1989; Logie, Del Sala, Wynn, & Baddeley, 2000). In TD 11-year-olds, articulatory suppression impairs memory of visually similar items, enhancing the VSE, more severely than phonologically similar items (Hitch, Woodin, et al., 1989). This implies that under suppression phonological encoding is not utilised to the same degree as visual encoding, meaning at this stage in development both methods are active and can be utilised. VSE is observed at all ages included in the current study, and should be taken into consideration if ratings of the visual similarity of items are available.

Visual skills are more advanced than spatial skills throughout development (Logie & Pearson, 1997). Simultaneous skills appear to develop faster than

sequential skills between the ages of 5 and 12 years (Logie & Pearson, 1997; Pickering et al., 2001). Sequential memories continue to develop until around CA 15 years, whereas visual simultaneous memory plateaus at around CA 11 (Isaacs & Vargha-Khadem, 1989; Wilson et al., 1987). In summary, visual memory develops faster and reaches adult-like levels by CA 11, whereas spatial skills continue to develop into adolescence. All abilities increase over childhood, and typically have reached adult-like levels by aged 11 years. Therefore, although abilities in these areas may be uneven in the younger age-group included in this study (4-8 years), they should be relatively constant in the older age-group (10-14 years). Uneven ability levels in these subsystems of memory function are also observed in individuals with genetic disorders, such as DS.

3.1.3 Visuospatial memory in Down syndrome

Individuals with DS are characterised as better at spatial than visual memory across the life span (Chapman, Schwartz, & Bird, 1991; N. R. Ellis, Woodley-Zanthos, & Dulaney, 1989; Laws, 2002). Furthermore, within spatial memory tasks individuals with DS between the ages of 7 and 18 years old, were better at sequential than simultaneous tasks compared to Peabody Picture Vocabulary test (PPVT) -matched TD individual (Lanfranchi, Carretti, et al., 2009). Both these ability profiles are the opposite of those described in TD individuals above. Individuals with DS aged 11 to 25 years were impaired on non-verbal location learning tasks compared to Differential Ability Scale (DAS) or SBIS-matched TD individuals, meaning spatial LTM was impaired for MA (Pennington, Moon, Edgin, Stedron, & Nadel, 2003; Vicari et al., 2000). However, low control spatial STM was MA appropriate across childhood and adolescence in the DS population, compared to individuals matched on the PPVT or the DAS (Lanfranchi

et al., 2012; Pennington et al., 2003). Although individuals with DS between late childhood and adulthood perform better at visuospatial than verbal memory tasks, studies have shown that in tasks that require higher levels of cognitive control the uneven performance between verbal and visuospatial abilities disappears and both abilities are delayed for the MA of the participants (Lanfranchi et al., 2012, 2004). Therefore, the control required for a task is implicated in the observation of the uneven cognitive profile associated with DS. It is also possible that the discrepancy between simultaneous and sequential memory abilities is due to a higher level of cognitive control required for simultaneous memory encoding than sequential.

A limitation of many studies of atypical populations is that, due to limited sample sizes, characterising change in ability levels over development is not possible. Some studies have carried out trajectory analyses and produced the following conclusions about visuospatial memory development in the DS population. Visual memory develops rapidly between age 4 and early adulthood, where it plateaus; therefore visual memory does not stop developing until the second decade of life in the DS population (Couzens et al., 2011). Spatial memory develops rapidly aged 4 to 10, and continues gradually improving over life, but is essentially developed by age 10 years (Couzens et al., 2011). Other longitudinal studies found no significant changes in spatial memory skills between 8 and 11 years of age, suggesting it may be developed earlier than age 10 in some individuals (Hick et al., 2005). These trajectory analyses are also examples of variability in cognitive development within the DS population.

No studies have examined the development of simultaneous memory abilities in people with DS, however studies have looked at visuospatial memory ability development. Within spatial memory abilities, spatial sequential memory

develops between 6 and 17 years of age in the DS population (Frenkel & Bourdin, 2009). Between the ages of 10 and 18 years it appears individuals with DS have a preference to encode information visually rather than verbally, which is comparable to TD individuals aged 4 to 7 years (Lanfranchi et al., 2014). Given that the MA of the individuals in this study was 5:09, this implies that individuals with DS have comparable preferential encoding methods to TD individuals of the same MA. In general, memory abilities appear to improve over time in individuals with DS. However, it is important to remember that in the DS population, as in the TD population, there is a great degree of individual variation. In previous studies of visuospatial memory in the DS population, the cognitive control required for tasks used was moderate to high, which affects outcomes more severely in the DS population than in TD individuals. To address this issue, the tasks used in this chapter relied on eye-tracking, a low demand methodology, to maximise the inclusion and performance of the participants with DS.

The development of memory is still in progress during childhood in both TD and DS populations. Most memory domains are functional at near-adult levels by between 11 and 15 years of age in the TD population. However, the relationship between CA and MA is non-linear in atypical populations (Hodapp et al., 1992; Shah & Frith, 1983). Therefore, it is also likely that memory domains develop with different trajectories. For this reason, it cannot be assumed that memory domains develop either synchronously with each other, TD individuals, or other individuals with DS. In addition to this, it is important to remember than when comparing DS and TD populations across development, the impairment observed in the DS group may appear to increase with time (Crombie & Gunn, 1998; Patterson et al., 2013). This is not because the abilities in the DS group do not improve, but because the

rate of improvement in the TD group is significantly faster, resulting in the exaggerated lag of abilities in the DS group.

3.1.4 Mouse models of Down syndrome and their contribution to the motivation for the study

Due to limits in ethical and methodological parameters when working with atypical populations, mouse models of DS can be used to examine behaviours in more controlled and repetitive conditions. This section outlines a specific study that influenced the design of the paradigms used in this chapter. The study examined immediate, 10-minute delayed, or 24-hour delayed recognition in a mouse model of DS, and was strongly influential for the LonDownS group, which aimed to replicate the findings in infants, children, and adults (Hall et al., 2016). The study familiarised mice with objects in space, where three objects were placed in three corners of a square environment and the mice were placed in the centre. Familiarisations to the objects were two 10-minutes sessions; test sessions lasted 10 minutes and were immediate (within 30 seconds), delayed by 10 minutes or delayed by 24 hours. Memory was expressed as time spent exploring the target object(s)/(time spent exploring target objects(s) + average time exploring distractors). This method of analysis resulted in a score between 0 and 1, a discrimination ratio, which if around 0.5 showed no difference from chance, whereas the closer to 1 the discrimination ratio was the more preference the mice showed for the target object(s), showing unimpaired memory function. If memory function was impaired, a discrimination ratio of closer to 0 was expected.

The first paradigm was object memory, where the three initial objects were different, and in the test trial one was replaced by a novel object, while the layout was the same. This paradigm also had an odour version, where the items were

identical but had different odours, as mice explore based more on olfactory than visual information. The second paradigm was object-in-place memory, where the three initial objects were different, and two exchanged positions in the test trial. The third paradigm was object location, where the three initial objects were identical, and one was moved into the empty corner in the test trial, altering the layout of the space. The results showed mice were impaired at object recognition memory at 10 minutes, but not immediately or after a 24-hour delay, the same result was seen in the odour-based task. Object-in-place memory was not impaired in the Tc1 mice at any time point. Object-location memory was not impaired at 10 minutes, the only time point assessed for this paradigm. The authors interpreted this as typical object STM and LTM, and typical object-in-place STM and LTM.

In order to best replicate the mouse study a paradigm was designed where eye-tracking was used to assess recognition of novel stimuli, with no explicit responses required. As the mouse was placed in the centre of the environment, each familiarisation of the eye-tracking paradigms started with a central fixation. A 10-minute exposure would not be realistic for humans, who would tire or become bored of this process, a long familiarisation time of 8 seconds was decided upon, as this is longer than most eye-tracking trials and is consistent with other paradigms in this thesis, see Chapter 6. To mimic the mouse experiment, there were only two familiarisation trials, and a single test trial, all of equal length. The initial study only aimed to mimic the immediate test trial condition and therefore there were no assessments following a delay.

3.1.5 The current study

The current study aimed to replicate results found in mouse models of DS in the human population. Specifically, the study examined the nature of object and

object-in-place STM. Although studies to date have shown the discrepancy between visual and spatial abilities, and sequential and simultaneous abilities, there are still unanswered questions. For example, how do these abilities relate to each other at lower levels of cognitive control and younger CA? To answer this question, the current study assesses simultaneous visuospatial memory at the lowest possible cognitive demand level by using eye-gaze; a minimally taxing measure that is frequently and successfully used with TD infants and individuals with ID.

Therefore, the primary aim of this study was to replicate the findings of Hall et al. (2016) in humans by assessing object and object-in-place immediate memory at the lowest possible level of control required for task engagement. The secondary aim was to assess the change in these abilities across development in a cross-sectional design. Although the mouse model did not show impaired object STM, intermediate object memory was impaired. The current paradigm included only immediate test trials; therefore the results are comparable to the mouse model STM. The fact that this paradigm was very low control and the data was in no way manipulated or actively maintained means this was a better measure of STM than WM. The mouse model described object STM as unimpaired, but the human literature describes visual memory as more delayed than spatial memory in the DS population. In addition to this, human studies have matched on MA-measures, whereas the current study matched on CA, suggesting that the ability levels will appear more delayed.

Therefore, although our paradigm is based on the mouse study, our predictions are not perfectly aligned with their findings. The primary hypothesis was that object memory would be impaired, but object-in-place memory would not be, compared to CA matched TD participants. The secondary hypothesis was that

the impairment in object memory would increase over development due to the exaggerated lag observed in the DS population abilities over time. Object memory is an assessment of visual memory, whereas object-in-place is an assessment of visuospatial memory.

3.2 Methods

3.2.1 Participants

Participants with and without DS were recruited as described in the Methods chapter. Forty-three participants with DS were recruited between the ages of 4 and 14 years old. Thirty-two TD participants were recruited between the ages of 4 and 14 years. Eight participants with DS and 5 TD participants were excluded due to failure to attempt or complete the tasks included in this study. The remaining participants were split into two groups, early and late childhood (Table 3.1). There were no significant differences in CA in each group between DS and TD participants. All participants had verbal MA and non-verbal raw scores assessed using the BPVS and pattern construction, respectively. The application and analysis of these tasks are described in Chapter 2 Methods and Population Characteristics. Instead of the standardised verbal MA from the BPVS the verbal score was decided to be more appropriate for this population.

Table 3.1 Mean and standard deviation (SD), CA, verbal score and non-verbal measures of the participants included in this analysis, and the N included in each assessment

	Early Childhood		Late Childhood	
	DS	TD	DS	TD
Mean CA in months (SD)	74 (20)	71 (20)	148 (22)	139 (19)
CA range	45-99	48-99	118-170	114-166
N (Female)	17 (10)	14 (10)	16 (9)	13 (7)
Mean BPVS verbal score (SD)	41 (17)	87 (22)	68 (18)	141 (15)
N (Female)	16 (9)	14 (10)	16 (9)	13 (7)
Mean Pattern construction raw score (SD)	6.6 (6.3)	26.4 (14.8)	12.8 (7.5)	40.1 (13.4)
N (Female)	13 (8)	14 (10)	16 (9)	13 (7)
Object Memory N (Female)	17 (10)	10 (7)	16 (9)	13 (7)
Object-in-place Memory N (Female)	15 (9)	13 (9)	16 (9)	13 (7)

3.2.2 Design

There were two tasks, the object and object-in-place eye-tracking memory tasks described in the Methods chapter. As described, each task consisted of three familiarisation trials followed by a test trial, followed by a further three

familiarisation trials and a second test trial. Although two test trials is a low number for an eye-tracking task, this paradigm was designed based on mouse model behavioural research of DS (Hall et al., 2016). In this paper, the authors gave the mouse models two 10-minute familiarisation periods in the test space with 3 objects, followed by either an immediate, 10-minute or 24-hour retention period before the mice were re-introduced into the test space. In the "novel object recognition" task the test space contained 2 familiar and 1 novel object(s). In the "object-in-place" task the test space contained the same 3 familiarised objects, but two of the familiarised objects had exchanged positions. In human studies it is not feasible to have a 24-hour delay period, indeed, even a 10-minute delay would not have been comparable to the mouse model as the human participants could not be confined to a sterile arena for 10 minutes. Due to the piloting nature of this paradigm and sample, it was decided that an immediate test trial presentation would be appropriate, and that two trials would be presented rather than one as in mice trials, to increase the likelihood of obtaining useful data. The effect of trial is not a subject of the hypotheses here, but was motivational in the original design of the paradigm. The familiarisation period was long for eye-tracking studies, to mimic the mouse model design, and thus it was determined that two trials would be a possible threshold of attention in younger participants.

The study had both within and between group factors. Between groups were the participant groups of DS and TD and the age-groups of early and late childhood. Thus, the independent variables were group and age-group. The dependent variable was a measure of looking time, calculated as described in 3.2.4 Analysis. The within group factor was the task, object or object-in-place memory. Trial, as in

first and second trial, are also within subject, but are not relevant to the hypotheses of this study.

3.2.3 Procedure

TD participants carried out all tasks on the same day, whereas participant with DS completed the BPVS and pattern construction on one day, and the eye-tracking tasks on a subsequent day within one month of the original test date. The eye tracking tasks are now described.

3.2.3.1 Object memory

Initially four objects were presented on the screen, their start size was 8° x 8°, they expanded and contracted to maintain attention. The four objects were matched on size, colour intensity, and familiarity; they were a slipper, spade, tambourine and sponge, see Figure 3.2. The objects were presented in the four corners of the screen for 8 seconds. Each familiarisation trial was separated by the presentation of a central stimulus that had to be fixated on before the task would continue; this ensured that participants were attending to the screen. After the third familiarisation trial, there was no central stimulus, the screen refreshed with a novel object replacing the study object in the bottom left corner. The novel object was a pineapple. The whole process then repeated: three familiarisation trials, followed by a test trial with the novel object in the top right hand corner to control for top-bottom or left-right bias. The test trials were presented for 8 seconds, and the whole procedure lasted 2 minutes. The outcome of this test is the percentage looking time to the novel object, as an indication of recognition of a novel object, and thus object memory.

Raw eye-tracking output consists of coordinates of each eye on the screen at approximately 120 samples per second or one sample every 8 milliseconds. To be

included in the analysis of this task, participants were required to have at least 1500 valid samples in familiarisation trials, and 100 valid test samples.

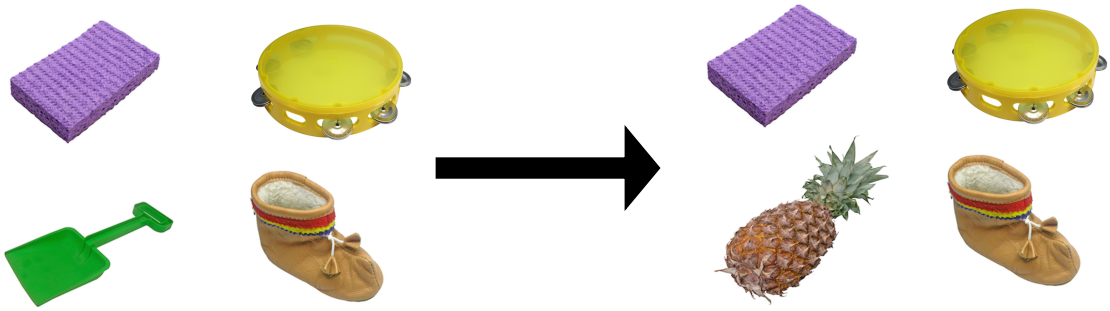

Figure 3.2 The stimuli for the object memory study trials and test trial, shown here in test trial 1 configuration, with the novel object in the bottom left

3.2.3.2 Object-in-place memory

Initially four objects were presented on the screen, their start size was 8° x 8°, they expanded and contracted to maintain attention. The four images were animals, matched on size, colour intensity and shape, see Figure 3.3. The objects were presented in the four corners of the screen for 8 seconds. Each familiarisation trial was separated by a central stimulus that had to be attended to before the task would move on. After the third familiarisation trial, there was no central stimulus, the screen refreshed and the same four objects appeared on screen but two of them had swapped positions on the screen. In the first test trial these were the two top objects. The familiarisation trials repeat, in the second test trial the two objects on the bottom were swapped. The test trials were presented for 8 seconds, and the whole procedure lasted 2 minutes. The outcome of this test is percentage-looking time to the animals in novel positions, as an indication of recognition of object-in-place change, and thus object-in-place memory.

To be included in the analysis of this task, participants were required to have at least 500 valid samples in familiarisation trials, and 50 valid test samples. The criteria for inclusion in this analysis was lower than in object memory as overall looking time was lower in this task than object memory.

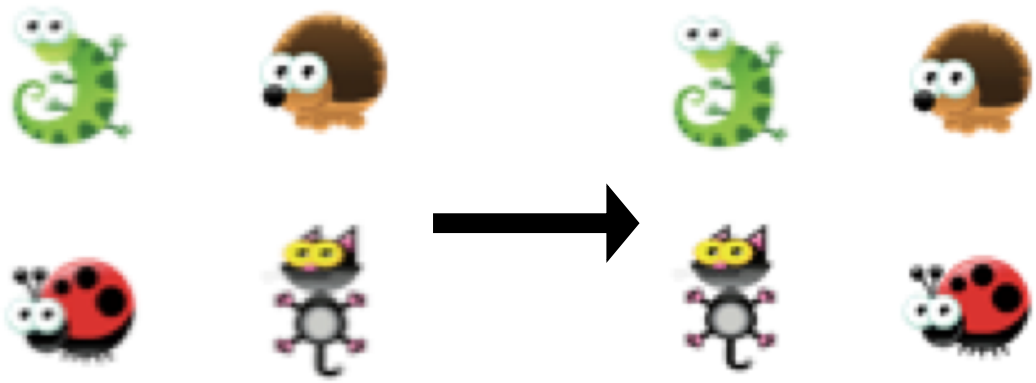

Figure 3.3. The stimuli for the object-in-place memory study trials and test trial, shown here in test trial 2 configuration, the two objects on the bottom have swapped locations

3.2.4 Analysis

Raw eye-tracking output consists of coordinates of each eye on the screen at approximately 120 samples per second or one sample every 8 milliseconds. All samples with missing data for either eye were excluded. The outcome variables were the total number of samples collected, the number of valid samples and the coordinates of the eyes at each valid sample. Therefore, the outcome was a "number of samples", rather than a measure of time. However, due to the positive linear relationship between sampling and time, it can be inferred that more valid samples in a trial correspond to longer a looking time, and the same logic for specific areas of interest. For this reason the outcome variables were referred to as "time" looking

to the screen or a specific area of interest. Statistical analyses were carried out with IBM SPSS Statistics, Version 20 (IBM, 2011).

Overall, looking times for familiarisation and test trials were the number of valid samples per trial. Due to significant differences in overall looking time across both familiarisation and test trials between groups, an alternative measure was used to compare results using proportional rather than absolute time. The screen was divided into four quadrants and percentage looking time (PLT) was calculated for the quadrant(s) of change using the coordinate data. PLT was the number of valid samples in the quadrant of change divided by the total number of valid samples for the trial. To compare the outcome equally for the two different tasks, the PLT of object-in-place memory must be halved. This is because the object-in-place memory analysis measured the PLT to two quadrants (two objects changed position), whereas the object memory task only measured one quadrant (one object changed). The formulas for calculating PLT for each task are below.

$$\textit{OBJECT MEMORY PLT} = LT_{QUADRANT\text{-}OF\text{-}CHANGE} / LT_{TOTAL}$$

$$\textit{OBJECT-IN-PLACE MEMORY PLT} = ((LT_{QUADRANT\text{-}OF\text{-}CHANGE\_1} + LT_{QUADRANT\text{-}OF\text{-}CHANGE\_2}) / LT_{TOTAL}) / 2$$

To determine the validity of the paradigm in assessing memory, the PLT variables for each task were compared to chance. In the object memory trials the quadrant of change was only a single quadrant of the screen, therefore when comparing the PLT to chance it was compared with 25%. In the object-in-place memory trials the quadrant of change was two quadrants as two items exchanged

places and are therefore novel, but as these values were halved PLT of object-in-place memory was also compared to 25%.

3.3 Results

The main hypothesis is addressed first, before analysing the object and object-in-place memory tasks separately. Both tasks are then compared to CA and MA measures. Unless explicitly stated otherwise, analyses are carried out on test trial data.

3.3.1 Task comparison

The primary hypothesis was that individuals with DS would be impaired on object but not object-in-place memory compared to TD participants. An ANOVA was conducted to examine the effect of group on looking to the target quadrant(s) over the two test trials in each task. Overall, the DS group looked significantly less to the quadrant(s) of change than the TD group, $F(1,50)= 4.46$, $p=0.040$, $\eta_p^2=0.082$. Within subjects there was a significant interaction between task and group $F(1,50)=4.80$, $p=0.033$, $\eta_p^2=0.088$. The interaction was driven by a group difference in the object memory task that was not present in the object-in-place memory task, shown in Figure 3.4.

This finding supports our hypothesis that the DS group would be comparatively impaired on the object memory task, but not the object-in-place memory task. There was also an unexpected significant interaction between trial and age-group, $F(1,50)=4.31$, $p=0.043$, $\eta_p^2=0.079$ in the combined analysis, which was not directly relevant to our hypotheses and so is not further discussed.

In summary, there was a significant interaction between group and task, caused by the impairment in the DS group in the object memory task that was not present in the TD group, supporting our primary hypothesis.

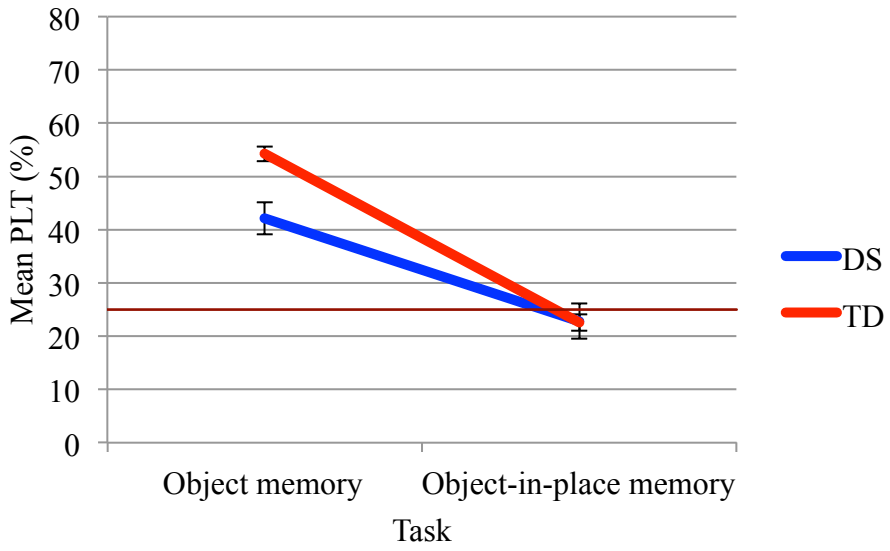

Figure 3.4 Mean PLT to target in object and object-in-place memory tasks of the DS and TD groups. Error bars represent +/-1 SE. Chance is marked with a horizontal line at 25%.

3.3.2 Object memory

The familiarisation trials are analysed first and then the test trials. T-tests were carried out to examine the difference in mean looking time to the screen, in the familiarisation trials the DS group looked significantly less at the screen than the TD group in both trials (trial 1: $t=-3.720$, $p<0.001$; trial 2: $t=-3.455$, $p<0.001$). For this reason the suitability of familiarisation as a covariate in further analyses was assessed. However, there was no linear relationship between familiarisation looking time and the dependent variables in groups or age-groups, meaning this was not a sensible analytical decision. The lack of relationship between familiarisation time and PLT is not surprising as the use of PLT was designed to control for the difference in overall looking times between groups.

The secondary hypothesis was that the impairment in object memory in the DS group would increase with age. A two-way ANOVA was conducted to examine the effect of age and group on PLT to the novel object. The DS group looked

significantly less to the novel object than the TD group, $F(1,52)=6.64$, $p=0.013$, $\eta_p^2=0.11$, shown in Figure 3.5. There was no significant effect of age-group ($F(1,52)=2.88$, $p=0.096$, $\eta_p^2=0.052$) or an age-group by group interaction ($F(1,52)=1.25$, $p=0.269$, $\eta_p^2=0.023$), indicating that object memory did not change over childhood significantly differently between groups. Including familiarisation looking time as a covariate did not alter the pattern of results (main effect of group: $F(1,43)=4.68$, $p=0.036$, $\eta_p^2=0.098$). These results do not support our hypothesis.

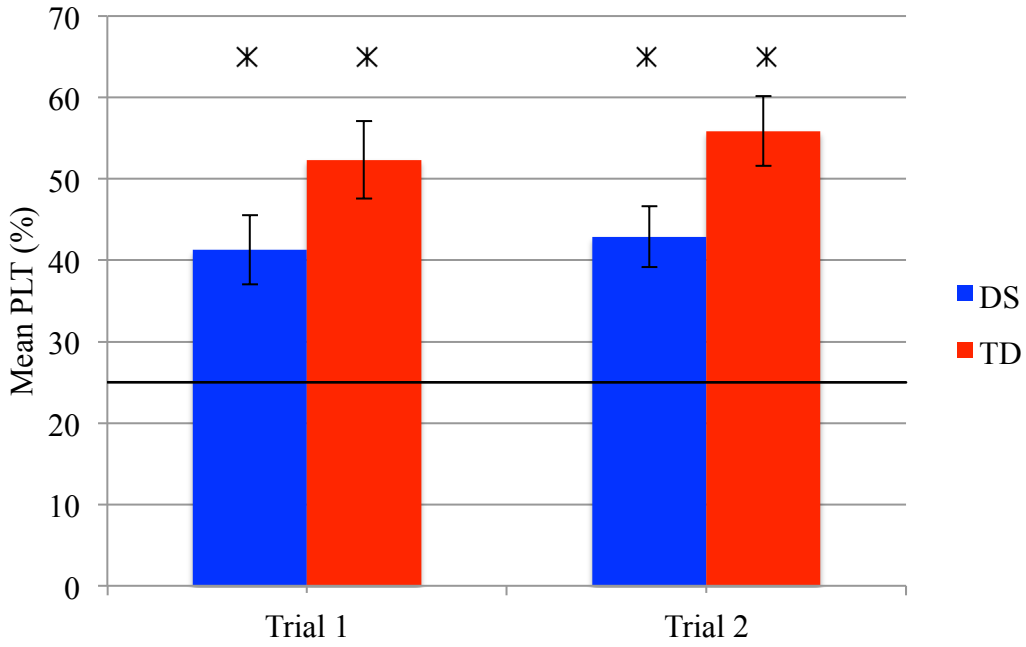

*Figure 3.5 Object memory PLT of DS and TD groups in trial 1 and 2, error bars represent +/-1 SE. Chance is marked with a horizontal line at 25, group means significantly above chance are marked with an *.*

In summary, participants with DS looked significantly less to the novel object than TD participants, supporting the hypothesis that object memory was impaired in participants with DS compared to TD individuals. There was no significant effect of age-group on this behaviour. Therefore, there was no statistical support for the

hypothesis that the object memory impairment increased with age. Both groups looked significantly above chance to the novel object, providing evidence that learning was taking place and memory was functioning in both DS and TD groups.

As the hypothesis was that the behaviour would change across age in different ways in the two groups, despite the lack of significance in the omnibus analyses, further investigation into this measure was carried out to illuminate if there were more subtle changes occurring. Within each age group a multivariate ANOVA was carried out to examine the effect of group on looking to the target across each trial. In early childhood there was a significant group by trial interaction, with the DS group looking significantly less to the novel object than the TD group ($F(1,25)=8.14$, $p=0.009$, $\eta_p^2=0.25$), as shown in Figure 3.6. No significant effect of group was observed in the late childhood group, ($F(1,27)=0.95$, $p=0.338$, $\eta_p^2=0.034$).

These figures imply that in early childhood there is a difference between the first and second trial that is required for the DS group object memory to function appropriately, i.e. for the DS group to perform above chance in the test trial. This could be interpreted as increased familiarisation, as both test trials are preceded by familiarisation trials. However, it could also be due to a slower overall processing of information, and it may be the delay between the initial test and the second test, rather than the information that was presented in that period. From the data collected it is not possible to ascertain if the familiarisation itself, or the elapsed time between trials, was responsible for the improved performance of the early childhood DS group in the second trial. The early childhood TD group and both late childhood groups performed above chance in the first test trial.

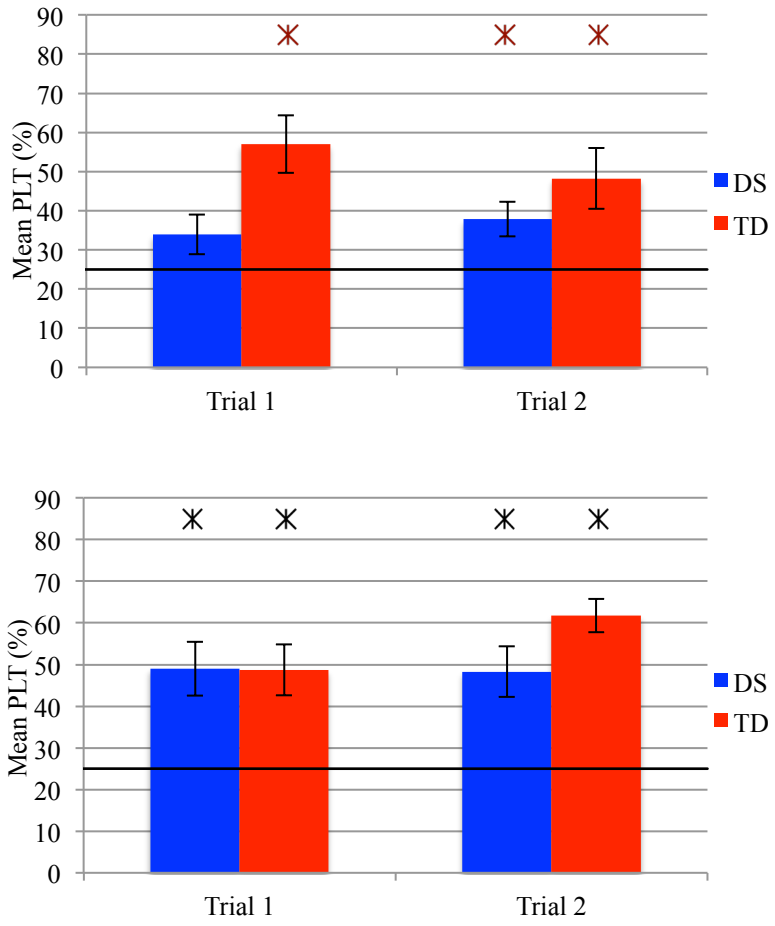

*Figure 3.6 Object memory PLT of DS and TD groups in trial 1 and 2 in early (top) and late (bottom) childhood. Error bars represent +/-1 SE. Chance is marked with a horizontal line at 25%, group means significantly above chance are marked with an *.*

3.3.3 Object-in-place memory

The familiarisation trials are analysed first and then the test trials. A t-test of the familiarisation trial data showed the DS group looked significantly less to the screen than the TD group in both trials (trial 1: t=-3.909, p<0.001; trials 2: t=-3.733, p<0.001). Familiarisation looking time as a covariate was examined, but as was observed for object memory there was no reliable linear relationship with PLT within group or age-groups. The affect of adding familiarisation time as a covariate

was examined to see if the looking time to the stimuli explained test performance, but as the data were converted to percentages, it is not unsurprising that this affect was not observed.

A two-way ANOVA was conducted to examine the effect of age and group on PLT in the test trials, there was no main effect of group, $F(1,53)=0.03$, $p=0.866$, $\eta_p^2=0.001$, see Figure 3.7. There was no main effect of age-group ($F(1,53)=1.30$, $p=0.260$, $\eta_p^2=0.025$), or group by age-group interaction ($F(1,53)=0.17$, $p=0.685$, $\eta_p^2=0.003$). When overall familiarisation looking time was included as a covariate the effect of group remained non-significant, ($F(1,52)=0.19$, $p=0.668$, $\eta_p^2=0.004$).

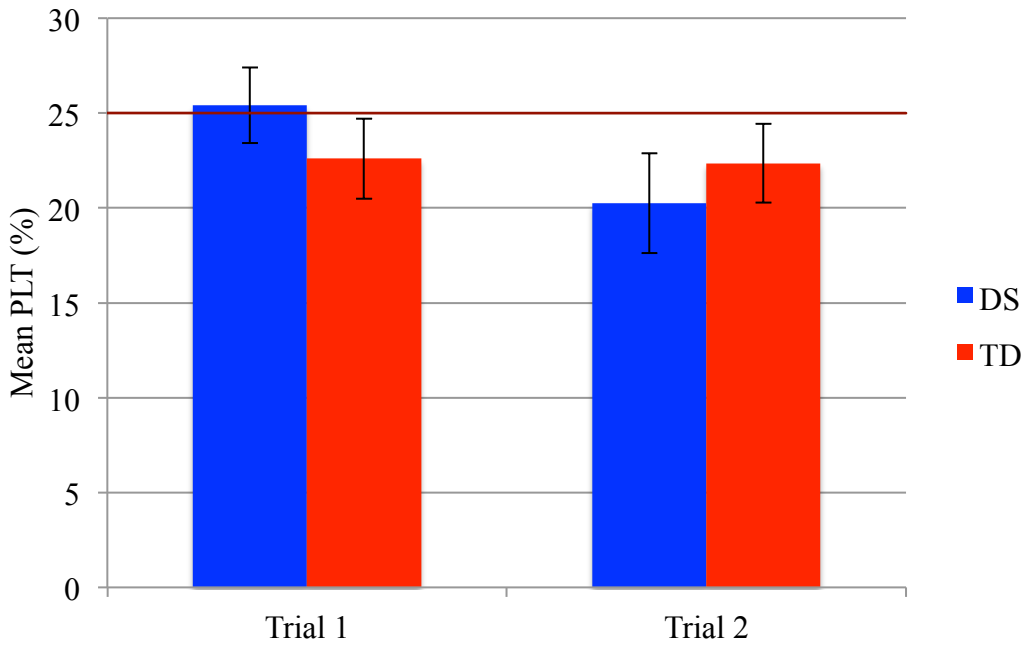

*Figure 3.7 Object-in-place memory PLT of DS and TD groups in trial 1 and 2. Error bars represent +/-1 SE. Chance is marked with a horizontal line at 25%, group means significantly above chance are marked with an *.*

In summary, no significant effect of group or age-group on object-in-place memory was observed and it can be concluded that the DS group were not behaviourally different to the TD group on the capacity assessed by this task.

However, it should be noted that no measures of PLT were significantly different from chance, implying that this paradigm did not detect object-in-place cognitive function as it was designed to. This could have been influenced by insufficient familiarisation times or insufficiently sensitive test measures, as will be discussed later. For this reason the further analyses that were carried out on object memory are not carried out here.

3.3.4 Correlations between object and object-in-place memory, CA and verbal and non-verbal measures

To assess if the behaviours in object and object-in-place memory tasks were associated with MA, correlations analyses were carried out. The PLT measures were averaged over the two trials in each task, producing one object memory measure and one object-in-place memory measure. Average PLT in object and object-in-place memory tasks were correlated with BPVS derived verbal score and pattern construction measures, as well as CA. The outcomes are reported in Table 3.2. No significant correlations were observed in either group. This is consistent with the theory that neither CA nor MA are associated with these measures of memory, supported by the absence of age-group effects observed in the previous sections.

Table 3.2 Correlation coefficients, significance and N's for object and object-in-place memory PLT scores and, respectively, CA, BPVS verbal score and pattern construction non-verbal raw score, split between DS and TD groups. CA in months

Group	Measure	Statistic	CA	Verbal score	Non-verbal raw score
DS	Object Memory	Pearson Correlation	0.251	0.16	0.319
		Sig. (2-tailed)	0.159	0.39	0.098
		N	33	31	28
	Object-in-place Memory	Pearson Correlation	0.017	0.099	0.186
		Sig. (2-tailed)	0.929	0.604	0.344
		N	31	30	28
TD	Object Memory	Pearson Correlation	0.188	0.021	-0.044
		Sig. (2-tailed)	0.379	0.929	0.841
		N	24	20	23
	Object-in-place Memory	Pearson Correlation	0.289	0.322	0.373
		Sig. (2-tailed)	0.152	0.144	0.060
		N	26	22	26

Note. No correlations reached statistical significance at the 0.05 level

3.4 Discussion

The primary hypothesis of this study was that object memory but not object-in-place memory would be delayed in the DS population compared to TD participants of the same CA. In support of this hypothesis a significant group by task interaction was observed, due to a difference between group outcomes in object memory abilities that was not present in object-in-place memory abilities. However, the effect size was small and so should be interpreted with caution. The secondary hypothesis was that the observed object memory impairment would increase over developmental time, due to the exaggerated lag in abilities in those with DS compared to TD individuals. Contradictory to this, there was no significant interaction effect of group and age-group on the object memory abilities.

The outcome that object memory was overall impaired in the DS population compared to TD individuals of the same CA was not novel in itself. What makes this result pertinent to the literature is the level of control required for the task used. According to the Cornoldi and Vecchi theory of memory, memory abilities are influenced both by the format of stimulus presentation and the control required to manipulate and encode the data presented (Cornoldi & Vecchi, 2004). Eye-gaze is the least control demanding methodology that could be used, enabling this study to investigate the abilities of individuals with DS at the lowest possible level of control. Our results suggest that, even at this low level, individuals with DS were impaired at object memory compared to CA matched TD individuals.

However, when comparing the results to chance, it was clear that the DS group still had functional object memory, as looking to the novel object was above chance. In early childhood, the DS group did not look to the novel object significantly above chance until the second trial. Therefore, although object

memory abilities were delayed, with longer exposures individuals with DS performed above chance. This was true of both trials in the late childhood DS group, where there was no significant effect of group. This suggests that life experience, which increases with CA, may contribute to the ability to identify novel objects. Both these findings have implications for the educational approach taken with children with DS. For example, the evidence here suggests that longer exposure to information, or repetitive exposures, could enable children with DS to learn visually presented information similarly to their TD peers. This result is supported by findings that Hebbian learning can occur in verbal and visuospatial domains in the DS population (Mosse & Jarrold, 2010). In addition to this, low-control object memory abilities, rather than diverging from the TD population across development, appear to converge, making them a relative strength in the DS population. This could be used to facilitate learning and improve outcomes.

Comparing these results to the results of the mouse study of object memory in the DS population, there are some complicated contradictions to consider. In the mouse study the mice had typical immediate object memory, impaired after 10 minutes, and typical again after 24 hours. This implies that the mouse model of DS has functional object STM and LTM, but impaired intermediate, or WM, abilities. Our finding in human participants was that object memory was impaired in STM, which contradicts the mouse models. There are multiple reasons this could be the case. Firstly, and most obviously, perhaps the relationship between mouse and human memory storage systems is not directly comparable. This difference in findings requires further comparisons to confirm the root of the conflict between the mouse and human results. Although the long familiarisation and test exposures were designed to be comparable to the mouse model literature, perhaps this was

more demanding or boring for human participants. A follow up study with shorter trials and shorter intervals between familiarisation and test trials might be more comparable to the mouse STM findings. Secondly, in the mouse study different mice were tested at different time points, i.e. no mice were assessed at both immediate and delayed trials. It is possible there was a group effect, with the mice in the immediate group having better overall memory abilities than the 10-minute delayed group, but this is unlikely. Therefore, although it would be interesting to investigate the effect of further delays on object memory in DS, it would not be comparable to the mouse literature as the same participant would be exposed to multiple assessments at different time points. Due to the high level of variability in ability level in individuals with DS, comparing memory abilities at different time points between individuals would not be a sound design. Overall, although the visual STM impairment result contradicts the mouse model, it agrees with the literature reports on the DS population, implying this may be a feature of DS that is not well replicated in mouse models.

A limitation of this paradigm was the finding that neither DS or TD groups, at any age or overall, looked to the novel object-in-place stimuli at above chance levels. This is a very simple paradigm, suggesting the TD individuals should have been able to recognise the change in object position in the test trials. Due to the lack of significant difference between chance and the looking times observed, it cannot be concluded that object-in-place memory was successfully assessed. Therefore, the results of this assessment are not discussed again in this thesis.

There was also a major design-based limitation of both tests used in this task. In the original mouse study, the mouse was placed in the center of the space in both the familiarisation and test trials. However, although there were central

fixation points before the familiarisation trials, there was no central stimulus preceding the test trial. Therefore, the location of the eyes on the screen was not controlled for in the beginning of the test trial, and any resultant data cannot be concluded to indicate memory function, as there was no interval between encoding and recognition. The fact that the screen simply refreshed suggests that, although memory could have been relevant, attention is more likely to be assessed by this paradigm. Future studies should include a central stimulus between familiarisation and test trials to ensure memory, rather than attention, is the cognitive outcome being assessed.

Due to the method of presentation of both familiarisation and test trials, there are further aspects of this study that could affect the results. The stimuli are presented in both study and test trials visually; therefore, it can be concluded that visuospatial memory is being assessed. The stimuli are presented simultaneously, which has been shown to be impaired in the DS population compared to sequential memory encoding abilities (Carretti et al., 2013). There are no instructions given to the participants to try and remember the stimuli, and the test trial follows immediately on the study trials. Therefore, there is no active assessment of LTM, but it is possible that the participants are using their LTM personal frameworks, as described in 1.4 Memory, to scaffold visuospatial memory, e.g. verbally labelling the objects from LTM, which would increase the memory storage systems encoding information. There is no way of currently controlling for, or assessing if participants used this technique, except for by taking CA into consideration. TD individuals transfer from preferential visuospatial encoding of stimuli, to verbal encoding at around CA 7 years (Palmer, 2000). Therefore, it is probable that the late childhood TD group were using some verbal encoding mechanisms. Studies of individuals

with DS have shown that they prefer a visuospatial memory encoding technique until later than TD individuals, up to 18 years of age (Lanfranchi et al., 2014). Therefore, although verbal memory techniques used in the task cannot be controlled for, it can be speculated that the DS and TD groups used non-identical mechanisms in late, and potentially to some degree, early childhood.

There is also the issue of STM vs. WM; the immediate presentation of trial 1 is an assessment of STM. However, repeating study and test trials a second time increased the likelihood that the participants were aware of the task, and more likely to purposefully encode the data. This means that trial 2 could rely on both WM and STM. The distinction between these two memory formats is complex and requires more clearly defined temporal restraints. The two trials are considered together as measures of STM rather than WM, due to the lack of explicit encoding or retrieval and the probability that participants were not consciously rehearsing the stimuli in a manner typical of WM functionality. Therefore, these paradigms assess simultaneous, visual and visuospatial STM.

An interesting future study to further examine the cause of the failure of the object-in-place paradigm would be to re-design the stimulus presentation format to address the issue. Instead of having the four stimuli, two of which change positions, it might be more comparable to the mouse literature to have three different stimuli in three corners of the screen, in the test trial two exchange position, still leaving the same empty quadrant. This would provide an overall measure of visuospatial memory. It would also be interesting to have a comparative measure of location, or spatial memory. This could be assessed with a paradigm similar to the object-in-place alterations described above, but with three identical stimuli, rather than different items. In the test trial one item would move into the empty quadrant,

changing the layout of the items, and thus the global location relationships between the items. Finally, it cannot be assured that some participants did not use verbal memory techniques to encode the stimuli. Verbal labelling would give an advantage to TD participants, especially in the late childhood group. One way of preventing any use of verbal memory to support this task would be to use abstract, or nonsense, stimuli. Alternatively, articulatory suppression could be used to minimise the potential contributions of the subvocal rehearsal techniques of verbal memory as has been done in other studies (De Beni et al., 2005; Pickering et al., 2001).

Another potentially interesting future study would be to investigate the method of encoding in the DS population over time. Although previous work has shown that visual is preferred to verbal labelling (Lanfranchi et al., 2014), this may dependent on different control, CA and MA levels. A paradigm to examine whether individuals are utilising verbal or visual memory encoding techniques could be designed as follows. The same display set as in the object memory paradigm, but present four objects that are either phonologically or visually similar, to test verbal and visuospatial encoding respectively. If the DS group performed better in one condition than another then it could be concluded they prefer that method of memory encoding. This could be carried out at different CA and MA levels to investigate any change in memory encoding techniques over time and ability levels.

Although behavioural abilities are usually predicted to improve over time and age, there are some possible explanations for the absence of correlations with CA or MA equivalent measures. For example, it is possible that these paradigms assess such basic cognitive skills that they have developed to adult-like levels in early development. It is also possible that the paradigm was too simple to capture change over developmental time sufficiently. A feature of atypical cross-sectional

population studies is that MA and CA may not appear to correlate with specific skills. This can be a reflection of a genuine plateau in skill development. However, if each participant were followed longitudinally then a correlation between CA and MA and other cognitive measures would generally be observed. Therefore, a lack of correlation between CA, MA and other cognitive measures should be interpreted with caution due to the nature of cross-sectional studies.

To conclude, there was a significant interaction between task and group that was driven by a group difference in abilities in the object memory task that was not present in the object-in-place memory task. These findings support our hypothesis that individuals with DS were comparatively impaired in object memory but not object-in-place memory. There was no significant interaction between group and age-group in visual STM, meaning our secondary hypothesis that the impairment in visual STM would increase over age had no statistical support. These conclusions only apply to low-level control STM abilities, not to higher control assessments or WM or LTM, which will be investigated statistically in Chapter 5 Visuospatial Working Memory and Long-Term Memory.

Chapter 4 Verbal Working Memory and Long-Term Memory

4.1 Introduction

In this section the definition of verbal memory and the theories behind different verbal memory functions and features are discussed. Features of verbal WM and LTM in TD individuals are described. The literature on verbal WM and LTM abilities in the DS population is reviewed, before discussing the current study.

4.1.1 Verbal memory

Verbal memory is the ability to acquire, retain and recall verbal data. This form of memory encodes spoken words and sounds, but can also be used to encode information that is not verbally presented (Baddeley, 1986, 1996). For example, when visually perceiving a black dog, labelling this image with the words "black dog", recodes the visual stimulus into verbal information. In typical adulthood this happens automatically and it is theorised that verbal memory is the preferential format for memory encoding from around age 7 onwards (Palmer, 2000). Before 4 years of age there does not seem to be a preferential method of memory encoding and from aged 4 to 7 years there is evidence that visuospatial memory is preferred (Palmer, 2000). However, throughout life both memory systems are required and are used in concert. To ensure that verbal memory is being assessed in an experimental environment either familiarisation or test of memory should include verbal components, especially in younger children who prefer other methods of data encoding. The only method that ensures verbal memory assessment is both familiarisation and assessment formats being verbal.

Language is integral to typical development, and without it humans would be incapable of encoding or manipulating verbal information. (Pungello, Iruka,

Dotterer, Mills-Koonce, & Reznick, 2009). In terms of learning and memory, for any verbal information to be encoded in LTM it must pass through the verbal memory domain of WM: referred to by one theory of memory as the phonological loop (Baddeley et al., 1998; Palmer, 2000). Although verbal memory also encompasses non-language based utterances, i.e. nonsense sounds, the majority of verbal memory requires formal language (Baddeley et al., 1998; Hick et al., 2005). The implication of the relationship between language and verbal memory abilities in development is that the deviance of one function from the norm will affect the development of the other and thus exaggerate the atypicality of both language and verbal memory abilities.

4.1.2 Theories of verbal memory

Retention of auditory stimuli past a few seconds is theorised to rely on the phonological loop, and heavily dependent on the left hemisphere of the brain (Baddeley, 1986; Logie et al., 2003). It is hypothesised that the phonological loop holds and rehearses verbal information, utilising the phonological store and sub-vocal articulation respectively. According to Baddeley, the phonological store is a short-term, phonologically based, limited capacity store that lasts in the order of a few seconds. When phonemic data enters the store it is temporarily retained with no effort, meaning very recently heard words are unconsciously retained and can be recalled with minimal exertion for very short periods of time (Baddeley & Hitch, 1977). Any storage or manipulation of verbal data beyond the immediate unconscious storage of the short-term store, involves the rehearsal loop of WM. If data are visually presented they must be recoded into a phonological format before entering the store and rehearsal domains (Baddeley, 2000). This recoding is theorised to rely on sub-vocal articulation (Baddeley, 1986; Baddeley et al., 1998).

The route the stimulus takes into memory, whether direct or requiring recoding, is important to consider when discussing processing, storage, and retrieval of data. This description only covers one of the main theories of memory function; many other contradictory and more recently developed theories exist (Atkinson & Shiffrin, 1971a; Cowan et al., 1999; Kane, Bleckley, Conway, & Engle, 2001). However, in this thesis the focus is on development of specific abilities, so this background is provided as a context through which to discuss results, rather than as a unanimously accepted theory. The features of the phonological loop and their experimental support are now reviewed.

The phonological nature of the loop is demonstrated by the phonological similarity effect (PSE). This is a phenomenon where verbal memory is worse for phonetically similar than dissimilar lists of words (Baddeley, 1966, 1968; L. K. Ellis, 1980). The same effect is not seen with lists of semantically similar words, supporting the theory that the loop relies on the sound of the word rather than the meaning of the word (Smith & Jarrold, 2014). Further to this, in lists with mixed similar and dissimilar phonemic words, the dissimilar stimuli are better recalled, showing the specificity of the effect even in simultaneous presentation of mixed stimuli (Lewandowsky & Farrell, 2008).

The limited capacity of the loop is demonstrated by the word length effect (WLE), a phenomenon where recall is worse for lists of longer words than shorter words (Baddeley et al., 1975). Essentially, memory span is inversely related to word length (L. K. Ellis & Hennelly, 1980). This is thought to be due to the increased time taken to rehearse each individual stimulus: if the rehearsal process occurs at a specific speed, then the longer the words take to rehearse, the fewer words can be rehearsed (Baddeley et al., 1975). The WLE is present in both visual and auditory

presentations of stimuli (Baddeley, Chincotta, Stafford, & Turk, 2002). However, in alternating lists of long and short words, total recall was equal to recall in pure short word lists (Hulme, Suprenant, Bireta, Stuart, & Neath, 2004). This result suggests that, although in pure lists the words are encoded by a single loop with limited capacity, it is possible that in mixed lists, different length stimuli are encoded by different loops, enhancing the capacity for both word length items. The authors theorised this improved recall of long words was due to the increased distinctiveness of the words, as opposed to the long words being surrounded by other long words, each is divided by a short word, making the environment of each long word more unique, and thus, easier to encode (Hulme et al., 2004). The theory of sub-vocal articulation is further supported experimentally by correlations between articulation rates and memory recall spans (Hitch, Halliday, & Littler, 1989; Hulme, Thomson, Muir, & Lawrence, 1984). Articulatory suppression, the practice of articulating a meaningless sequence during experimental measures of verbal memory, oblates the WLE by preventing rehearsal (Hitch, Halliday, & Littler, 1989). Theoretically, if articulatory suppression does not alter the verbal memory span of lists of different word lengths then rehearsal is not yet occurring in that individual.

Depending on the method of presentation of the stimuli, memory encoding can be interrupted by different mechanisms. These findings support the theory that memory domains are functionally distinct. For example, if the stimuli are visually presented then articulatory suppression removes the WLE (Baddeley et al., 1975). When the stimuli are presented simultaneously in both visual and auditory formats there is no effect of articulatory suppression, implying the visuospatial and verbal WM systems work complementarily to rehearse information, and that together the

methods of memory storing can compensate for interference experienced by one or another system (Baddeley et al., 1975). Therefore, although the two WM systems are functionally distinct, they can work collaboratively to store data even in conflicting environments.

The literature frequently discusses the U-shaped curve of verbal WM, which is a phenomenon where the first and last items in the list are recalled preferentially to the middle items (Hitch, Woodin, et al., 1989; Hulme et al., 2004; Hurlstone et al., 2014). It is hypothesised that the earlier items in the list are preferentially recalled due to longer rehearsal time, an effect called "primacy", and the later items are preferentially recalled due to the "recency effect". Some degree of this preferential recall is also observed in LTM (Talmi, Caplan, Richards, & Moscovitch, 2015; Talmi & Goshen-Gottstein, 2006). Memory for the middle items, which are not subject to preferential encoding, is thought to be the most genuine measure of LTM and referred to as mid-list recall (Hurlstone et al., 2014). The development of all three effects of preferential recall is assessed in this study.

Verbal WM is a capacity-limited, short-term and phonologically defined system for storing, rehearsing and manipulating verbal information. WM is a current process, which lasts not longer than around 10 minutes and therefore should be tested within this time window (Palmer, 2000). For data to move from WM to LTM it must be encoded and stored. Given the two features of verbal WM: storage and rehearsal, and the relatively passive nature of the store, it was theorised that rehearsal rates must be influential on the transference of data from WM to LTM storage (Hitch, Halliday, & Littler, 1989). This was equated to: the longer an item is in WM, the more likely it is to be transferred to LTM. This implies that, in an auditorily presented list of words, the earlier items in the list are more

likely to be stored in LTM. Thus, the first items in the list should be better recalled than the mid-list items, and the mid-list items should be better recalled than later list items, however, the recency effect contradicts this theory. Although recency is an interesting phenomenon, since the 1970s it somewhat fell out of style until around 2005, leading to a gap in the literature (Baddeley & Hitch, 1977; Talmi et al., 2015; Talmi & Goshen-Gottstein, 2006). For this reason, much of the work on this phenomenon is old.

The implication of the recency effect is that recall of recently experienced information is improved for a short period of time. Given that recency is the improved recall of most recent items, it could be presumed that this relies on STM. Baddeley and Hitch (1977) argued against the idea of recency being a primarily STM reliant faculty by showing that simultaneously presenting two different stimuli sets in different formats, visual and auditory, did not oblate the recency effect in either task (Baddeley & Hitch, 1977). This suggests that the participants were using multiple formats of memory encoding and storage that each displayed recency effects. The authors stated that recency was not exclusive to free-recall in STM and was also involved in the WM system (Baddeley & Hitch, 1993). Indeed, this argument was strengthened by the work of Watkins and Peynrcoglu, who presented multiple stimuli forms alternatingly (e.g. riddles, sounds and object), and found a recency effect was observed independent of the stimuli form assessed, implying the three stimuli sets were stored separately, despite their overlapping temporal presentation (Watkins & Peynrcoğlu, 1983). Therefore, recency has longer lasting effects than those of STM, and can occur in multiple different memory formats simultaneously, indicating an improved recall of recently presented data, and reducing the reliance on time available to rehearse the information.

There is strong evidence for this effect in verbal WM tests, but the effect in LTM is less clearly demonstrated (Hitch, Woodin, et al., 1989). Some studies have shown that in delayed trials, later list items are recalled less well than most other items, rejecting the theory of LTM recency (Craik, 1970; Craik, Gardiner, & Watkins, 1970; Craik & Watkins, 1973). This even occurred when the participants were specifically instructed to focus on the last four words, including when they were given an interval to overtly rehearse these stimuli (Craik & Watkins, 1973). The authors theorised this is related to the *type* of rehearsal, rather than if rehearsal has occurred (Craik & Watkins, 1973). In this study the authors refer to a weak 'phonemic' rehearsal, remembering the sound of a word, as opposed to stronger and more complex semantic-associative rehearsal, where data are encoded in multiple forms. The conclusion was that, although rehearsal may enhance the recency effect in WM, it does not guarantee LTM encoding of data. A degree of associative memory rehearsal appears necessary to ensure that data are encoded and stored in LTM (Thaler et al., 2013). Thus, when considering preferential recall of items dependent on their position in the sequence, it is also important to consider whether rehearsal could occur, and, if possible, what form of rehearsal.

Conversely, other authors have found evidence in support of a recency effect in LTM. The "continuous distracter" technique, where distractors such as backwards counting or anagram solving separate each stimulus, might be presumed to oblate recency effects by preventing overt or subconscious rehearsal of items. However, the results of studies that employed this technique have shown that even in environments of high interference, later items are recalled preferentially to other list items, which the authors report as support of a genuine LTM recency effect (Bjork & Whitten, 1974; Talmi & Goshen-Gottstein, 2006). These findings should be

interpreted with caution, although the authors of these studies report the results as LTM, the period of delay was 15 seconds and thus these findings appear to support the presence of recency effects in WM, rather than LTM. These authors also argue for the effect of recency in real-life LTM, such as recall of sports scores and parking spaces (Bjork & Whitten, 1974). However, it is clear that these memories are complex associative memories, and these findings do not contradict the previously discussed theory of the *type* of rehearsal, rather than the quantity, that is influential to the memory storage system.

4.1.3 Verbal memory in typical development

In TD verbal memory, individuals have better span for meaningful sentences, on average 16 words, than for unrelated word or digit lists, on average 7 words (Baddeley & Levy, 1971; Baddeley, Vallar, & Wilson, 1987; Miller, 1956). Verbal span increases over CA in the TD population (Isaacs & Vargha-Khadem, 1989). In addition to auditory or written data, other forms of data can be recoded into verbal memory (Baddeley, 2000). Studies of the TD population show that individuals start verbally labelling images between the CA of 5 and 7 years, at the same developmental stage that articulatory rehearsal commences (Conrad, 1971; Flavell, 1970). Although it may undergo development, it is likely the phonological store is present in some degree from infancy, allowing the mimicry of verbal stimuli and learning of language (Lynch, Oller, Steffens, & Levine, 1995). Impairments were noted in phonologically similar vs. dissimilar visually presented sequences from above 5 years of age onwards (Conrad, 1971; Hitch, Woodin, et al., 1989). However, in other groups of 5-year-olds this effect was not observed (Hitch et al., 1983). The PSE is not reliably observed in visually presented and verbally labelled stimuli until aged 7 years (Henry, 1991). Further work confirmed that if stimuli are visually

presented the PSE is not robustly observed until around aged 7 years (Hitch et al., 1983; Hitch, Halliday, Dodd, & Littler, 1989; Palmer, 2000). There is some controversy around the stereotypical age of onset of this effect, variation in which is attributed to different teaching methods in childhood (Henry & Conners, 2008; Lanfranchi et al., 2014). Overall, the PSE can occur if the stimuli are auditorily presented from age 5 years, but is not reliably observed in visually presented data until around age 7 years, supporting the theory that verbal encoding is not preferential until this age, and suggesting the recoding of visual information does not reliably automatically happen until this age.

Experimental findings in childhood related to rehearsal are as follows. The capacity of the phonological loop increases from 4 to 7 to 10 years of age, and at each age-group the individuals are affected by WLE, implying rehearsal is available to some degree at these ages (Henry, 1991; Hulme et al., 1984). In a study of individuals age 6 years, the WLE was observed if the stimuli were presented auditorily but not visually, whereas 7, 8 and 10 year old participants displayed the WLE in both presentation formats (Hitch et al., 1983; Hitch, Halliday, Dodd, et al., 1989). Support for the involvement of rehearsal in the WLE comes from findings that there is a direct relationship between articulation rate and verbal recall abilities at ages 8, 10 and 12 years old (Nicolson, 1981). Gathercole and Adams (1992) also observed this in 2 and 3-year-olds, suggesting variable age-of-onset of this feature of memory. The fact that WLE can be observed in children before the certainty of rehearsal functionality implies that limitations of the phonological store also contribute to the WLE. In support of this, no WLE is observed if output delays are uniform for different length stimuli, which controls for the length of rehearsal that could be performed (Henry, 1991), implying the store itself is limited to some

degree in childhood. Articulatory suppression has no effect on memory span at age 5 years, but does by 10 years of age, suggesting rehearsal is not occurring at aged 5 (Hitch et al., 1983). Further to this, articulatory suppression does not equally oblate the WLE from the ages of 8 to 11 years, implying the WLE, and rehearsal, are still developing over this period (Hitch, Halliday, & Littler, 1989). Overall, the WLE occurs if the stimuli are auditorily presented from age 4 years, but is not observed in visually presented data until around aged 7 years, and rehearsal abilities continue to develop further into adolescence, as evidenced by uneven effects of WLE in this period.

The WLE and PSE are observed in a percentage of TD individuals from age 4 onwards, but not robustly until 7 years of age (Henry, 1991). These results provide evidence for the emergence of verbal WM in early childhood, from CA 4 years, and the majority of TD children automatically verbally label visual data and display the PSE and WLE by around 7 years of age (Gathercole & Adams, 1993; Henry, 1991; Hitch, Woodin, et al., 1989).

TD individuals are thought to encode verbal data in "chunks", usually limited to around four items per "chunk" (Cowan, 2010). Thus, separating the presentation of data by temporal or visual spaces appears to benefit TD verbal memory abilities by permitting chunking (Farrell, 2012). In typical development chunking appears to spontaneously arise between 4 and 8 years old, but if data are presented in pre-chunked formats, younger individuals can still benefit from this effect (Towse, Hitch, & Skeates, 1999). This applies to both visually and auditorily presented data.

Verbal WM abilities are also related to LTM by the familiarity of the words presented (Gregg, 1976; Hulme et al., 1997). In other words, if a word is well known and stored in LTM, then it is more likely to be successfully recalled in verbal WM

tasks. This applies throughout childhood and adulthood, and is supported by amnesic cases who fail to recognise familiarised words that have been created after the traumatic injury, or the onset of retrograde amnesia (Corkin, 2002; Majerus & Linden, 2003).

4.1.4 Verbal memory in Down syndrome

Individuals with DS are delayed on verbal WM tasks compared to TD participants matched on a range of verbal and non-verbal measures, from childhood to adulthood (Jarrold & Baddeley, 1997; Jarrold, Baddeley, & Phillips, 1999; Marcell & Armstrong, 1982; Vicari et al., 1995). When this was initially described, the first question to be answered was whether this was verbal STM specific or if all STM abilities were impaired in the DS population and other genetic syndromes. These hypotheses were both disproved by the evidence that individuals with DS, whilst MA delayed in verbal tasks, perform at or above MA levels in spatial STM tasks, and the finding that other syndromes have opposing distributions of relative behavioural strengths and weaknesses (Annaz, Karmiloff-Smith, Johnson, & Thomas, 2009; Lanfranchi et al., 2004). Although these results show the DS population were still delayed compared to their CA, they indicated the uneven cognitive profile of development, and the importance of characterising these profiles rather than assuming global delay across all faculties. People with DS have high rates of auditory and speech production impairments that could cause the verbal WM impairment (Purser & Jarrold, 2005). This was elegantly disproved by studies showing hearing and speech levels, although contributing to verbal memory abilities, do not fully explain the observed delay (Baddeley & Jarrold, 2007; Jarrold et al., 2002). Based on the Baddeley model of memory abilities, it then seems the phonological loop function is implicated in this impaired verbal WM function. This

implies that the phonological store, articulatory rehearsal, or both, are in some way functionally impaired in people with DS.

In a free recall assessment of auditorily presented stimuli, there was no significant difference between the recency effect displayed by participants with DS of mean CA 13:07 and controls MA-matched with the SBIS (Vicari, Marotta, & Carlesimo, 2004). Another study found no significant difference in recency effects, but significantly worse primacy and mid-list recall in the DS group of mean CA 16:07 compared to controls MA-matched on Wechsler intelligence scales (WAIS/WISC) (Carlesimo et al., 1997). Recency was also observed in short lists of 3 or 4 words in DS groups with mean CA 13:10 or 18:08, compared to controls MA-matched on the BPVS or RCPM (Jarrold et al., 2000; Purser & Jarrold, 2005). These findings support the theory that decay of verbal information is not significantly different between DS and controls matched on verbal or non-verbal measures. In summary, MA-appropriate recency effects have been demonstrated in adolescence and adulthood in DS groups. Primacy effects and mid list recall are attenuated in adolescents with DS. Neither effect has been investigated in childhood or across development.

Verbal WM is experimentally assessed using lists of digits or words. In children and adolescents with DS the average digit span was 3.5 digits, which is impaired compared to non-verbal intelligence-matched TD participants (Bird & Chapman, 1994). Studies have shown that digit span in the DS population was related to language abilities, and not significantly different from TD participants matched for MLU (Seung & Chapman, 2000b). Therefore, verbal WM in the DS population was appropriate for MLU, a measure of language abilities, illustrating an

association between the development of language and memory in the DS population.

The harder version of the digit task is backwards digit span, which places higher demand on executive function and cognitive control than the forward task. Performance on this task was more impaired than forward span in participants with DS compared to TD individuals (Vicari et al., 1995). Therefore, increasing the cognitive load, or demand on executive function, impaired verbal WM capacity in participants with DS.

The total number of words produced in verbal fluency tasks was significantly associated with verbal WM abilities in the DS population (Stavroussi, Andreou, & Karagiannopoulou, 2016). Semantic memory performance, as measured by verbal fluency, was not significantly impaired in the DS population compared to TD individuals matched on general cognitive ability (Laws, 2002; Pennington et al., 2003; Vicari, Bates, et al., 2004), but was impaired if matched on BPVS (Nash & Snowling, 2008). Therefore, matching on verbal measures removes the impairment seen in verbal WM, but reveals impairment in semantic verbal fluency. Furthermore these verbal fluency and WM abilities were related in the DS population. These findings support an association between language abilities and verbal WM in the DS population, and provide more evidence for the uneven cognitive profile of abilities in the DS population compared to TD individuals.

Participants with DS age 9 to 30 years old displayed the PSE although to a lesser degree than TD individuals matched on BPVS (MacKenzie & Hulme, 1992; Smith & Jarrold, 2014). Articulation speed had no effect on verbal memory for either short or long words suggesting an absence of rehearsal, and a WLE was observed in serial but not probed recall in participants with DS (Jarrold et al.,

2000). The mean BPVS MA of these participants was 4:06, which is younger than the MA when these effects are seen in the TD population. This implies that CA, and thus life experience, may play some role in the development of techniques and methods used when engaging in verbal WM tasks. This does not support the theory that the development of these methods fully correlates with overall cognitive ability. The authors of this study concluded that, although it did not appear that the participants engaged in sub vocal rehearsal, there was no evidence for the absence of this behaviour being the cause of verbal WM impairment (Jarrold et al., 2000).

Studies have shown that participants with DS do not benefit from the auditory presentation of verbal data to the same degree as TD individuals, and therefore display a smaller difference in verbal WM abilities dependent on in the data are presented auditorily or visually (Marcell & Armstrong, 1982; Marcell & Weeks, 1988). The preferred method of visual presentation of stimuli is as objects, not written words, due to the impaired reading skills of many people with DS (Byrne et al., 2002). The simultaneous presentation of stimuli in auditory and visual forms can improve verbal recall abilities of participants with DS, particularly if the assessment is verbal (Jarrold et al., 2002; Laws, MacDonald, & Buckley, 1996).

A study of 25 individuals with DS of a mean CA 12:06 years compared verbal WM abilities to two control groups matched on either PPVT-R derived vocabulary or WISC derived MA (Duarte et al., 2011). The study assessed digit span, but also examined the difference in verbal WM abilities influenced by input and output methods. Verbal memory was assessed by tasks with verbal input and output (verbal-verbal), visual input and verbal output (visual-verbal), and verbal input and visual output (verbal-visual). Digit span and verbal-verbal were overall impaired in the DS group; whereas verbal-visual and visual-verbal abilities were not impaired

compared to vocabulary matched controls, but were compared to MA matched controls (Duarte et al., 2011). Digit span correlated with verbal-verbal and visual-verbal abilities in the DS group. Therefore, verbal encoding and verbal retrieval abilities were vocabulary appropriate, if the information was also either presented or assessed with a visuospatial feature, in the DS population between 7 and 18 years of age.

Previous studies of verbal WM in participants with DS have utilised comparable methodologies to this study and obtained the following results. A study of 15 people with DS of a mean CA 16 years (MA from Wechsler intelligence scales: M=9:01, SD=2.5), presented a list of 20 words visually and read aloud by the participant or experimenter, followed by 40 stems, 20 from the learned list and 20 novel stems (Carlesimo et al., 1997). Stem-completion and the effect of priming were not significantly different in the DS and TD MA-matched participant groups. This stem-completion task demonstrates what the authors describe as typically behaving verbal implicit LTM in the DS population. In addition to this, the participants were tested on a word-learning task where 12 words were presented orally from either a related or unrelated list. Each list was presented and the participant's ability to recall the words was immediately tested, this was repeated five times. The recall of participants with DS improved over the trials at a similar rate to the TD group but total recall was significantly impaired (Carlesimo et al., 1997). Following a 15-minute interval another free recall of the list was assessed, the DS group were significantly worse than TD individuals in this trial (Carlesimo et al., 1997). Following the free recall the experimenter read a list of random words interspersed with those that had been learnt. The DS group were significantly impaired on identifying familiar words and had a significantly higher false hit rate

(Carlesimo et al., 1997). However, the "rate of information loss" or decay in memory abilities was not significantly different to the TD group (Carlesimo et al., 1997). This was the first study to show that verbal LTM abilities were impaired in the DS population. Therefore, the rate of learning and forgetting in the DS population were comparable to those seen in intelligence-matched TD individuals, and implicit verbal LTM appeared appropriate for the MA of the individual. However, both WM and explicit LTM recall and recognition of verbal information were impaired in the DS population compared to intelligence-matched TD individuals. It should be noted that the MA of the DS group was higher than is frequently observed in cross-sectional studies, and this may make the results of this study non-generalisable to the DS population.

Another study used 14 participants with DS, mean CA 21 years, to investigate explicit and implicit LTM (Vicari et al., 2000). These individuals were MA-matched to a TD group using the L-M SBIS (DS: *M*=6:05, SD=0.76; TD: *M*=6:03, SD=0.82). Fifteen printed words were read aloud by the participant or experimenter, 30 stems were presented of 15 familiarised and 15 novel words. Again there was no significant difference between the DS and MA-matched TD group's performance on this task (Vicari et al., 2000). Ten minutes later the familiarised words, along with 15 novel words were presented and the participants had to identify if each word was familiar or unfamiliar. Participants with DS correctly recognised significantly fewer words and had significantly more false hits (Vicari et al., 2000). In addition to this, verbal WM was assessed with word list learning, 12 words were simultaneously auditorily and visually presented and then the participant was immediately tested on this list, five times sequentially. The score here was the total number of words, and the DS group scored significantly

lower than TD individuals (Vicari et al., 2000). Development of abilities over the five trials was not analysed. Therefore, although explicit WM was impaired in participants with DS for intelligence-MA and CA, implicit LTM, as measured by stem completion, appeared intelligence-MA appropriate.

Another study assessed verbal memory abilities of participants with DS aged 10-17 years, compared to TD participants age 4-11 years with no specific matching criteria (Jarrold et al., 2007). The MA of the DS group was 5:04 derived from the BPVS. Four faces were presented with forenames and surnames. After familiarisation trials there were three immediate verbal recall trials, where the score was the number of separate (forename/surname) names recalled. Each name was then presented simultaneously with three distractor names, and the recognition of the correct name was recorded. The DS group were better at verbal recognition than recall, indicating uneven performance across different task demands, but both measures were significantly impaired compared to standardised CA TD scores (Jarrold et al., 2007). This study carried out a transformation of the data where the scores were converted to z-scores and regressed against the log-transformed values of CA, BPVS MA and RCPM MA of the TD group to provide an 'expected' score value. The observed recognition and recall verbal ability values were subtracted from the expected, producing scores than can be directly compared across tasks. However, neither recall nor recognition of verbal data were significantly impaired compared to BPVS MA matched TD, or RCPM MA matched TD scores (Jarrold et al., 2007). Therefore, explicit verbal LTM abilities developed in-line with cognitive faculties such as receptive language and non-verbal abilities in DS individuals (Jarrold et al., 2007), whereas in the previous study, explicit verbal LTM was impaired for overall intelligence abilities. These contradictory results

highlight the importance of being very explicit about MA matching and data transformation methods applied (Vicari et al., 2000).

These studies have illustrated the overall cognitively appropriate development of verbal learning and forgetting, and impaired WM and LTM recall of verbal information for CA and intelligence. The latter study contradicted the previous work by finding verbal LTM abilities were MA appropriate, indicating the literature is not united on the ability level of verbal LTM in the DS population. However, a limitation of many of the previous studies has been the tasks used. For example, although words have been presented simultaneously visually and auditorily, the demand of reading the word may interfere with the encoding process. Therefore, a better task would reduce the cognitive load or demand on the participants with DS, enabling a more accurate measure of the memory abilities themselves, rather than other cognitive mechanisms. This study uses an alternative method of data presentation to maximise the potential for lower functioning individuals, as is now described, along with the hypotheses and aims of the current study.

4.1.5 The current study

Previous studies have assessed the change in verbal WM over multiple trials, and implicit verbal LTM using stem priming. In this study, three immediate trials of verbal WM were used, simultaneously presenting the stimuli visually (as images not words) and auditorily, to maximise the accessibility of the data to participants with DS. A delayed trial was also included as a measure of verbal LTM. Previous studies have focused on adolescence and adulthood; this study contributes to the literature by including younger CA individuals, and thus increasing understanding of a larger developmental time window.

Based on the findings of Purser and Jarrold (2005) and Carlesimo et al. (1997), it was hypothesised that, although the DS group would be impaired overall on verbal WM and LTM, the development of both measures and rates of learning and forgetting would be comparable to the CA-matched TD group. Based on Vicari (2004) and Carlesimo et al. (1997), it was hypothesised that the primacy effect would not develop across age, whereas the recency effect would change with age comparably to the TD group. Due to the effect of language on verbal memory, the correlations with verbal fluency abilities, and the non-significant differences in digit span between DS and MLU-matched TD individuals (Seung & Chapman, 2000a), the relationship between the dependent variables, digit span, verbal fluency, verbal, and non-verbal scores were also investigated.

The current study includes younger CA participants than any previously mentioned, therefore it was necessary to choose a methodology that was more age appropriate and would yield more information by not excluding low functioning participants. For these reasons, this study used the BAS 2 measure of verbal memory, which involved visually presenting the stimuli in a 4 x 5 grid format. This means that, although the items would be sequentially named, there may be different effects that influence the recall of items. For example, although recency is a strong effect in lists presentation, it is possible that particular spatial areas of the grid may be better recalled than others. For this reason, as well as the recency effect in both WM and LTM, the affects of spatial features that may influence recall were also examined, specifically if items in the corners, or on the edges, of the grid, were better recalled than mid-grid items.

4.2 Methods

4.2.1 Participants

Participants with and without DS were recruited as described in 2.2 Participants. Forty-three participants with DS were recruited between the ages of 4 and 14 years old. Thirty-two TD participants were recruited between the ages of 4 and 14 years. Twelve participants in the DS group were excluded due to failure to attempt or complete the task. Nine of the excluded participants with DS were in the early childhood group and the remaining 3 were in the late childhood group. Therefore, the groups consisted of 31 participants with DS and 32 TD participants, split into early and late childhood as shown in Table 4.2.

4.2.2 Procedure

The main focus of this chapter is immediate and delayed verbal memory, which was assessed using the BAS 2 components as described in 2.4.3.2 Components of the British Ability Scales (Second edition) (Elliot, Smith, & McCulloch, 1997). This task was chosen as it was applicable to the desired CA range, and it allowed assessment of verbal memory abilities with an added feature of visuospatial encoding, which has previously been shown to improve recall in individuals with DS. The participant was initially guided through the images and asked to name each one, and then the experimenter and the participant went sequentially through the grid verbally naming the images together twice. The experimenter then instructed the participant “now I’m going to take the pictures away and I want you to remember as many as you can”. The grid was then overturned, and the participant was asked, “tell me as many pictures as you can”. If this instruction was not understood then the experimenter, whilst pointing to the reverse of the grid said, “what was on here, can you tell me?”. If further

encouragement was needed the experimenter used various methods including “tell mummy, what’s on here”, or prompting by saying, “there was a…”. When the experimenter concluded that no further answers would be provided, the experimenter said “well done! That was really good. Let’s do it again and see if we can remember even more”. The experimenter and participant then re-iterated the names of all images once more, the experimenter overturned the grid and said, “tell me as many pictures as you can” or “what was on here?”. This second protocol was repeated a third time, resulting in 3 immediate measures of explicit verbal WM. After the third administration of this task, an interval of at least 15 minutes, but no more than 25 minutes, elapsed. Following this interval, the participant was presented with the stimulus grid faced down on the table and again asked, “Do you remember all those pictures you saw? There were a lot on one card and you had to remember them all. Can you tell me the pictures?”. The participant was encouraged in a similar manner to in the immediate test session. This assessment provided a measure of explicit verbal LTM. Although there was a tendency for the TD participants to recall the stimuli in a serial manner, whereas the participants with DS were more random or ‘free’ in their recall, both mechanisms are thought to rely on similar processing and are thus still comparable (Spurgeon, Ward, & Matthews, 2014). The TD participants had a time limit of 60 seconds to free recall the items. No strict time limit was imposed on the DS group as in some cases the time taken to encourage a single response was greater than 60 seconds. When this was the case only a single answer was accepted, and no individual was given longer than 2 minutes of answering time. This is an example of problems associated with applying a test normed on the typical population to atypical individuals. It was decided that it was more meaningful to permit extra time to the participants with

DS and collect the maximum amount of data, rather than to adhere strictly to the administration guidelines of the task and lose precious information. However, the interpretation of these outcomes should be tentative due to this idiosyncratic administration.

Although this procedure may appear like it makes the data non-comparable, there are good theoretical reasons for permitting this alteration of the limit. In the standardised assessment, immediately after administering the instructions, the experimenter starts the 60 seconds that the participant is permitted to answer. In the DS population, many individuals required further verbal clarification, encouragement, and prompting rather than the initial instructions. In addition to this, during the following minute many participants with DS became distracted, or bored, and required further prompts. These delayed prompts did not repeat the initial target of the verbal fluency task (animals), but were no-descript, along the lines of "can you think of any more?" or, "yes, a [previously named animal], and a [previously named animal], what else can you think of?". These changes in interaction between participant and experimenter would have reduced the potential reaction time for the participant, therefore although in many cases the one minute limit was adhered to, when necessary the participant was allowed an extra period of time to permit them to produce any data.

In addition to this task, digit span, pattern construction and the BPVS were administered as in Chapter 2 Methods and Population Characteristics (Elliot et al., 1997; E. Miller, 1984). Verbal and non-verbal MA equivalents were derived from the BPVS and pattern construction, respectively. Verbal fluency was also assessed as described below.

4.2.2.1 Verbal fluency

Verbal fluency is a measure of frontal cognitive function (Elfgren & Risberg 1998). Verbal fluency tasks have been used in many studies investigating cognitive abilities of individuals with DS. Several studies have found no significant difference in the total number of animals named in one minute between individuals with DS and MA-matched TD controls (Carney et al., 2013, Lanfranchi et al., 2010, Pennington et al 2003). However, Rowe (2006) reported that individuals with DS name fewer animals than MA-matched participants with non-DS ID. This implies that verbal fluency ability may be more related to MA than CA in the DS population, whereas those with other forms of ID verbal fluency may be more related to CA. Furthermore, adults with DS and dementia have been reported to perform poorer on a verbal fluency task than those without dementia (Ball et al., 2008). Indicating that verbal fluency assessments may rely to some degree on memory function, or the structures underlying this ability are specifically impaired early in dementia.

In this verbal fluency task participants were asked to name as many animals as they could in 1 minute (with previous described alterations). All animals named were recorded. Outcomes include the number of unique animals named (including age and sex variations). With participants who found the instructions too complex, they sang “Old MacDonald”, and were encouraged to name new animals each time, this was always recorded and the results are included. This task takes one minute. Inclusion in this task required verbal ability, although some participants were permitted to sign rather than verbally name animals, again this was always recorded.

4.2.3 Design

The study had both within and between group factors. Between groups were the participant groups of DS and TD and the age-groups of early and late childhood. Thus, the independent variables were group and age-group. Within groups were the changes in dependent variable outcomes over time. There are multiple dependent variables outlined in Table 4.1, and calculated as below.

PRIMACY_WM= (MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 1}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 2}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 3}}$)/3

MIDLIST_WM= (MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 4}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 5}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 6}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 7}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 8}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 9}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 10}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 11}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 12}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 13}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 14}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 15}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 16}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 17}}$)/14

RECENCY_WM= (MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 18}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 19}}$ + MEAN (TRIAL 1 + TRIAL 2 + TRIAL 3) $_{\text{ITEM 20}}$)/3

PRIMACY_LTM= ((TRIAL 4) $_{\text{ITEM 1}}$ + (TRIAL 4) $_{\text{ITEM 2}}$ + (TRIAL 4) $_{\text{ITEM 3}}$)/3

$$MIDLIST\_LTM = ((\text{TRIAL } 4)_{\text{ITEM } 4} + (\text{TRIAL } 4)_{\text{ITEM } 5} + (\text{TRIAL } 4)_{\text{ITEM } 6} + (\text{TRIAL } 4)_{\text{ITEM } 7} + (\text{TRIAL } 4)_{\text{ITEM } 8} + (\text{TRIAL } 4)_{\text{ITEM } 9} + (\text{TRIAL } 4)_{\text{ITEM } 10} + (\text{TRIAL } 4)_{\text{ITEM } 11} + (\text{TRIAL } 4)_{\text{ITEM } 12} + (\text{TRIAL } 4)_{\text{ITEM } 13} + (\text{TRIAL } 4)_{\text{ITEM } 14} + (\text{TRIAL } 4)_{\text{ITEM } 15} + (\text{TRIAL } 4)_{\text{ITEM } 16} + (\text{TRIAL } 4)_{\text{ITEM } 17})/14$$

$$RECENCY\_LTM = ((\text{TRIAL } 4)_{\text{ITEM } 18} + (\text{TRIAL } 4)_{\text{ITEM } 19} + (\text{TRIAL } 4)_{\text{ITEM } 20})/3$$

Table 4.1 The variables measured in this chapter and the assessment they are derived from, along with the minimum and maximum scores possible or achieved

Task	Dependant variable	Minimum	Maximum
Immediate verbal (each trial)	Average N of items recalled	0	20
Immediate verbal (overall)	Average N of items recalled	0	60
Immediate and delayed verbal (primacy, mid-list, recency)	Average N item in each block was recalled	0	1
Delayed verbal	Total N recalled after delay	0	20
Delayed verbal (decay)	Mean N recalled LTM as a percentage of mean N in third immediate verbal	0 %	150 %*
Digit span MA	Months standardised to TD population	2:06	18:00
Verbal Fluency	Raw score: N of animal names	0	36*
Verbal score	Ceiling item-errors made	12	160*
Non-verbal measure	Pattern construction raw score	1	63

Note. *= No actual maximum, values represent maximum values achieved in the study

4.2.4 Analysis

The primacy, mid-list and recency effects in WM and LTM were calculated as above. Digit span raw score was calculated as the ceiling value with the number of errors subtracted (Elliott, 1996). Verbal fluency was measured as the overall number of animals produced (E. Miller, 1984). Statistical analyses were carried out with IBM SPSS Statistics, Version 20 (IBM, 2011).

4.3 Results

4.3.1 Participant characterisation

The raw and converted scores of the DS and TD groups in early and late childhood are presented in Table 4.2. Unfortunately the early childhood TD group mean CA of the group was significantly different from the MA calculated from digit span ($t(15)=-4.49$, $p<0.001$, $\eta^2=0.573$). In the late childhood group the difference was non-significant. This suggests that the TD early childhood sample is not representative of the global population in these measures. Therefore, comparisons between these overall scores are non-informative, although relationships between these measure and other cognitive abilities between groups may still prove informative.

Table 4.2 The mean and standard deviation (SD) CA, digit span MA, and verbal fluency raw scores, verbal and non-verbal measures of all participants included in this analysis, and the N included in each assessment

	Early childhood		Late childhood	
	DS	TD	DS	TD
Mean CA months	81.85	71.19	146.94	139.63
(SD)	(22.19)	(20.57)	(23.60)	(18.80)
N	13	16	18	16
Mean Digit Span	55.63	90.19	61.18	162.75
MA months (SD)	(10.50)	(25.62)	(3.49)	(52.58)
N	8	16	17	16
Mean Verbal Fluency raw score (SD)	5.42 (3.57)	11.75 (4.94)	7.94 (3.63)	21.81 (6.46)
N	12	16	18	16
Mean Verbal	46.31	88.38	68.72	143.69
Score (SD)	(19.62)	(20.85)	(15.78)	(14.52)
N	13	16	18	16
Mean Non-Verbal	6.50	28.38	13.35	40
raw score (SD)	(6.13)	(14.87)	(7.64)	(13.35)
N	10	16	17	16

4.3.2 Overall difference in immediate verbal memory

A two-way ANOVA was conducted to examine the effect of age and group on overall immediate recall, there was a significant effect of group with the DS group recalling less than the TD group, ($F(1,59)=86.19$, $p<0.001$, $\eta_p^2=0.594$). There was also a significant effect of age, where the early childhood group recalled significantly fewer items than the late childhood group ($F(1,59)=25.978$, $p<0.001$, $\eta_p^2=0.306$). There was also a significant interaction effect between the group and age-group factors indicated that the groups improved at significantly different rates over time ($F(1,59)=12.771$, $p=0.001$, $\eta_p^2=0.178$). This significant difference in immediate verbal recall between groups over time appeared to be driven by a smaller increase in total verbal recall in the DS group from early to late childhood (early childhood: M=12.92; late childhood: M=15.78), than the TD group (early childhood: M=23.63; late childhood: M=39.88), as shown in Figure 4.1. These results support the hypothesis of impaired verbal WM, but do not support the hypothesis of similar development.

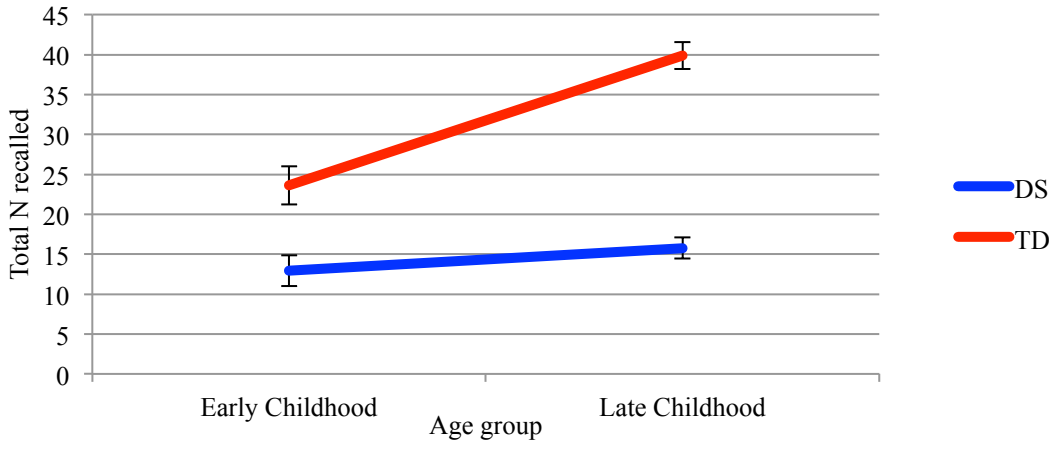

Figure 4.1. Mean total N recalled in the three immediate verbal trials in DS and TD groups over early and late childhood. Error bars represent +/- 1 SE

4.3.3 Differences in the three immediate verbal memory trials

A repeated measures ANOVA was conducted to examine the effect of age and group on immediate verbal recall over three trials, there was a significant interaction between recall and group ($F(1,59)=9.09$, $p=0.004$, $\eta_p^2=0.133$). The interaction between recall and age-group was borderline significant ($F(1,59)=4.02$, $p=0.050$, $\eta_p^2=0.064$). However, the three way interaction between recall, group, and age-group, was non-significant, meaning there was not a significant difference in the change in rates of learning across the three trials between age-groups, between groups, ($F(1,59)=0.17$, $p=0.682$, $\eta_p^2=0.003$), as shown in Figure 4.2. Therefore, although overall learning was significantly different between groups, within group changes over development were comparable.

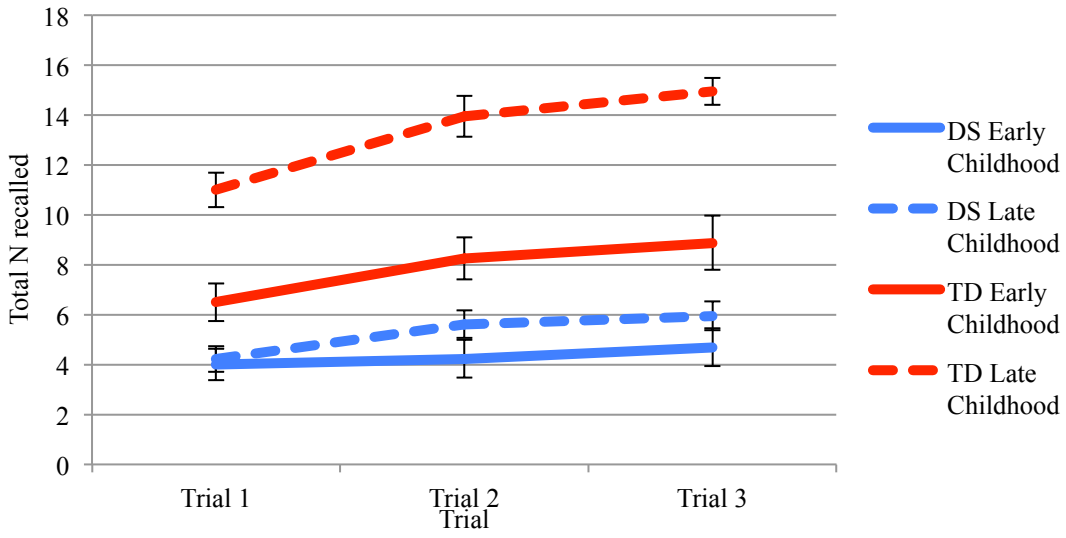

Figure 4.2. Mean N recalled in each of the three immediate test trials in each age-group in DS and TD groups. Error bars represent +/- 1 SE

4.3.4 Primacy, mid-list and recency effects in the immediate verbal memory trials

A multivariate ANOVA was conducted to examine the effect of age and group on primacy, mid list recall, and recency effects. For both primacy ($F(1,59)=4.31$, $p=0.042$, $\eta_p^2=0.068$), and mid list ($F(1,59)=14.27$, $p<0.001$, $\eta_p^2=0.195$) recall the interaction effects of group and age group were significant, implying these effect developed significantly differently across age in the two groups. However, there was not a significant interaction of age and group in recency recall, indicating this behaviour develops in a comparable manner in both groups, ($F(1,59)=0.362$, $p=0.55$, $\eta_p^2= 0.006$). The effect of group was significant in all three measures (primacy: $F(1,59)=24.87$, $p<0.001$, $\eta_p^2=0.297$, mid list: $F(1,59)=85.62$, $p<0.001$, $\eta_p^2=0.592$, recency: $F(1,59)=12.4$, $p=0.001$, $\eta_p^2=0.174$), and the effect of age was significant in both mid-list recall ($F(1,59)=21.51$, $p<0.001$, $\eta_p^2=0.267$), and recency ($F(1,59)=19.24$, $p<0.001$, $\eta_p^2=0.246$), but not in primacy($F(1,59)=2.65$, $p=0.109$, $\eta_p^2=0.043$).

These results suggest the groups did not improve comparably across age in primacy, as shown in Figure 4.3, or in mid-list recall, as shown in Figure 4.4. However, it appears recency affect in verbal WM improved comparably across age in both groups, as shown in Figure 4.5.

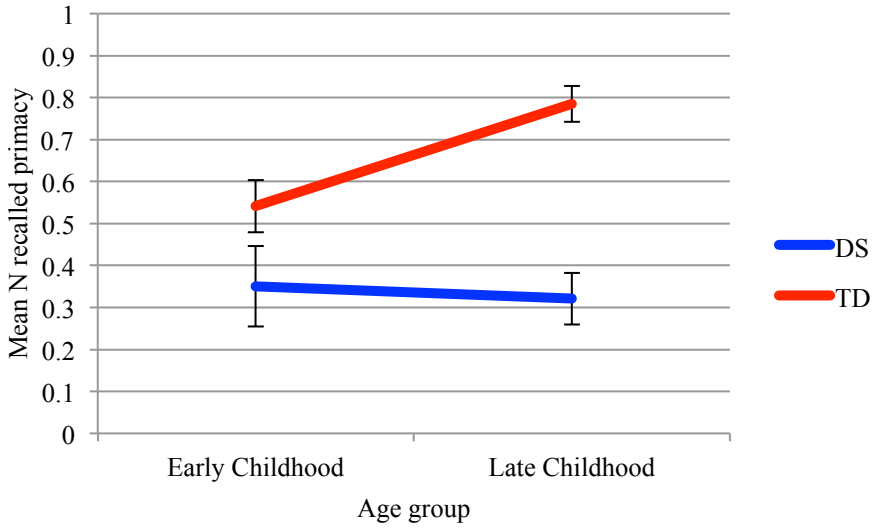

Figure 4.3. Mean N recalled in the first 3 items presented over the three immediate verbal trials. Error bars represent +/- 1 SE

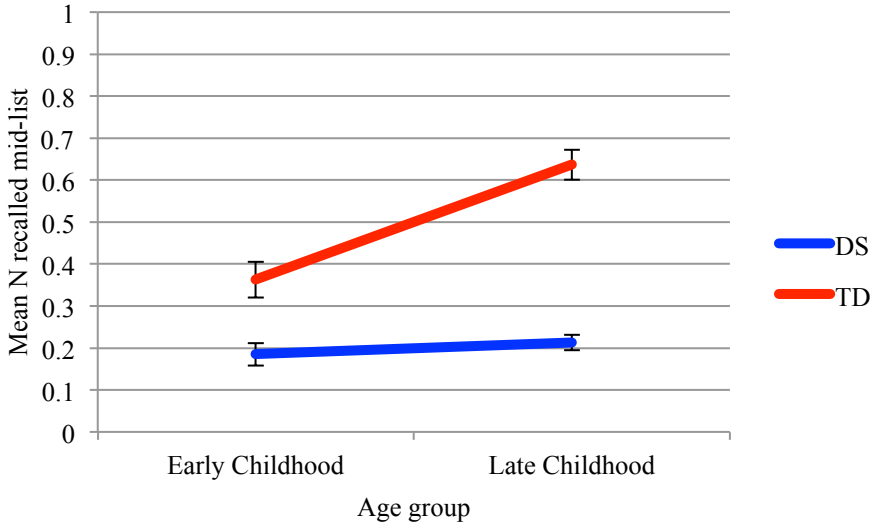

Figure 4.4. Mean N recalled in the middle 14 items over the three immediate verbal trials. Error bars represent +/- 1 SE

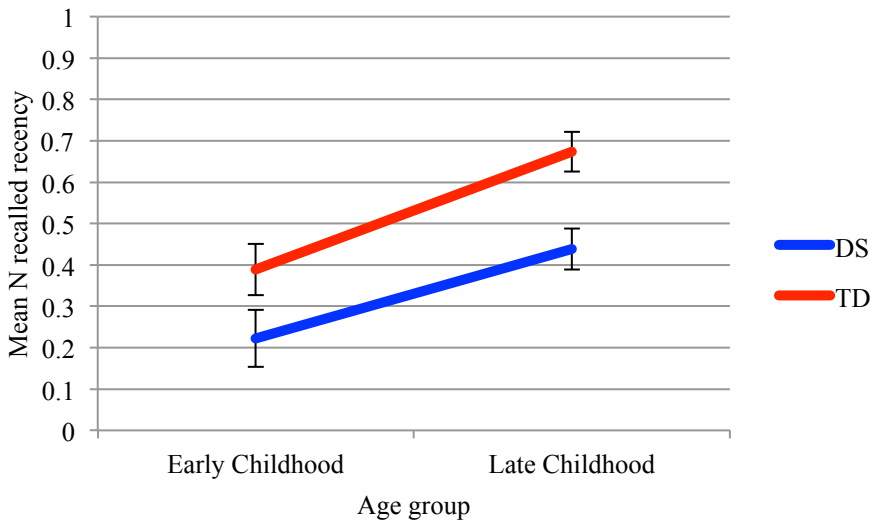

Figure 4.5. Mean N recalled in the final 3 items over the three immediate verbal trials. Error bars represent +/- 1 SE

4.3.5 Overall difference in the delayed verbal memory trial

A two-way ANOVA was conducted to examine the effect of age and group on delayed verbal recall, the effect of group was significant, the DS group were impaired ($F(1,59)=43.076$, $p<0.001$, $\eta_p^2=0.422$). There was a significant effect of age with better recall in the late childhood group ($F(1,59)=20.722$, $p<0.001$, $\eta_p^2=0.260$). However, the interaction was not significant, implying that verbal LTM improved comparably across age in both groups ($F(1,59)=2.50$, $p=0.119$, $\eta_p^2=0.041$), as shown in Figure 4.6. These results support the hypotheses of overall impaired verbal LTM, and similar development.

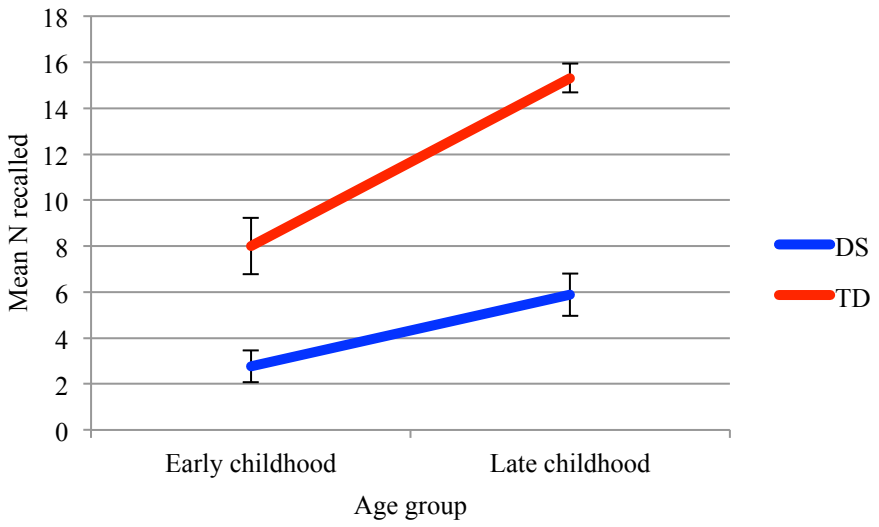

Figure 4.6. Mean N recalled in the delayed verbal trial (trial 4) in DS and TD groups over early and late childhood. Error bars represent +/- 1 SE

4.3.6 Primacy, mid-list and recency effects in the delayed verbal memory trial

A multivariate ANOVA was conducted to examine the effect of age and group on primacy, mid list recall, and recency effects in verbal LTM. For mid list ($F(1,59)=4.58$, $p=0.037$, $\eta_p^2=0.072$) recall the interaction effects of group and age

group were significant, implying this effect developed significantly differently across age in the two groups. However, there was not a significant interaction of age and group in either primacy ($F(1,59)=0.092$, $p=0.763$, $\eta_p^2=0.002$), and recency ($F(1,59)=0.000$, $p=0.997$, $\eta_p^2= 0.000$) recall. The effect of group was significant in all three measures (primacy: $F(1,59)=21.49$, $p<0.001$, $\eta_p^2=0.267$, mid list: $F(1,59)=39.93$, $p<0.001$, $\eta_p^2=0.404$, recency: $F(1,59)=18.29$, $p<0.001$, $\eta_p^2=0.237$). The effect of age was also significant in all three measures (primacy: $F(1,59)=8.88$, $p=0.004$, $\eta_p^2=0.131$, mid list: $F(1,59)=19.81$, $p<0.001$, $\eta_p^2=0.251$, recency: $F(1,59)=8.97$, $p=0.004$, $\eta_p^2=0.132$).

These results indicate that the groups improved comparably across age in primacy LTM as shown in Figure 4.7, and recency LTM, as shown in Figure 4.9, but that the development of mid-list LTM, a more genuine measure of LTM abilities, was not comparable between groups, as shown in Figure 4.8.

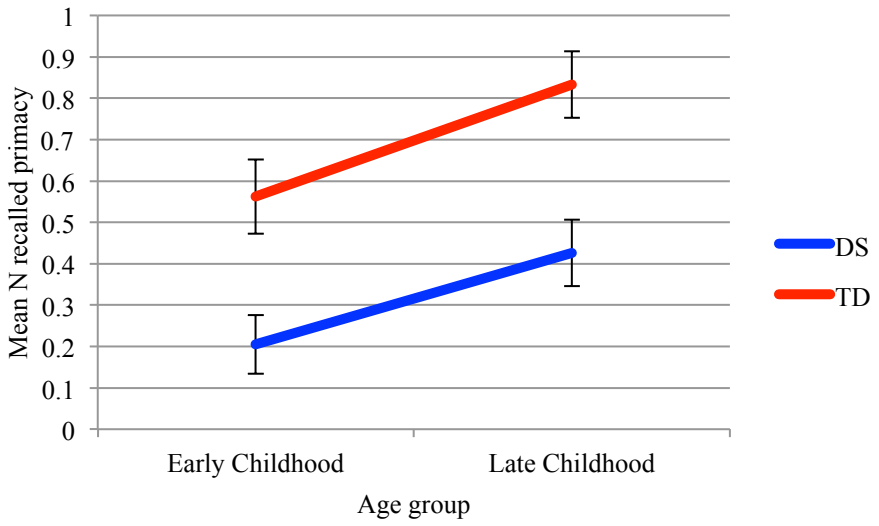

Figure 4.7. Mean N recalled in the first 3 items presented in the delayed verbal trial (trial 4). Error bars represent +/- 1 SE

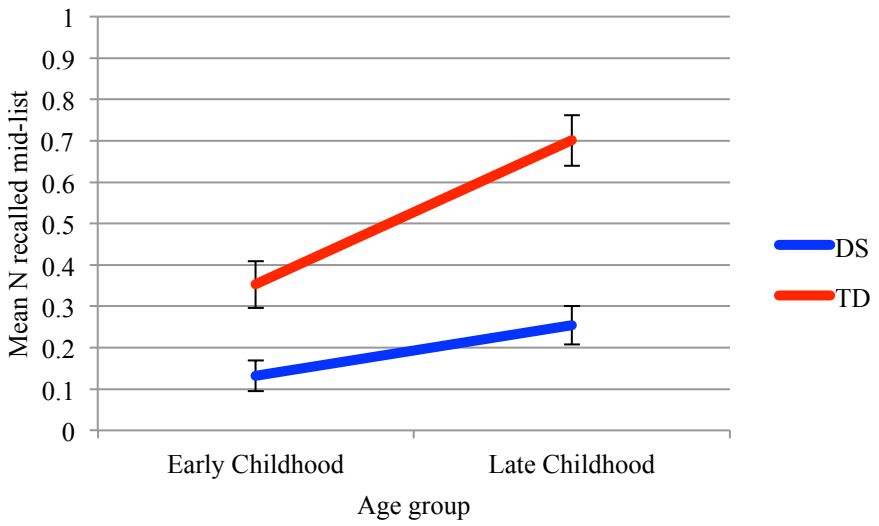

Figure 4.8. Mean N recalled in the middle 14 items presented in the delayed verbal trial (trial 4). Error bars represent +/- 1 SE

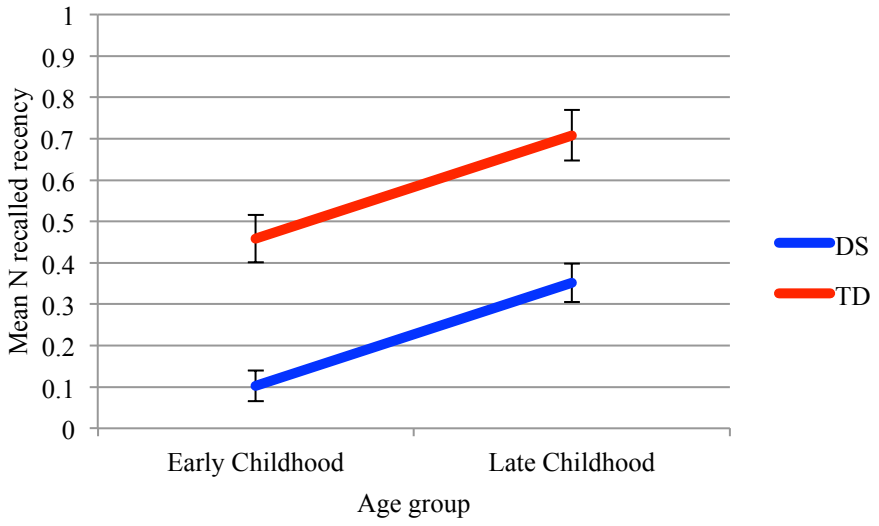

Figure 4.9. Mean N recalled in the last 3 items presented in the delayed verbal trial (trial 4). Error bars represent +/- 1 SE

4.3.7 Rates of decay from immediate to delayed verbal memory trials

To examine the relationship between verbal WM and LTM in DS and TD groups, the third immediate verbal trial (trial 3) and the delayed verbal trial (trial 4) outcomes were compared. The difference between trial 3 and 4 is referred to as decay, the loss of information over time. The change in this decay is how it alters over age. A multivariate ANOVA was conducted to examine the effect of age and group on recall in the third immediate trial and the delayed verbal trial. The DS group were significantly impaired compared to the TD group, indicated by a main effect of group ($F(1,59)=63.91$, $p<0.001$, $\eta_p^2=0.520$). There was also a significant difference in recall in early and late childhood ($F(1,59)=25.04$, $p<0.001$, $\eta_p^2=0.298$). The change in decay across age-group (interaction between group and age across trials) was significantly different between groups, ($F(1,59)=5.81$, $p=0.019$, $\eta_p^2=0.09$), as shown in Figure 4.10. The three-way interaction of group by age-group by trial was not significant, indicating the change in N recalled over WM and LTM was not significantly different between groups over time, $F(1,59)=1.01$, $p=0.318$, $\eta_p^2=0.017$. On examining the data, it appeared that by late childhood in both groups around 100% of the items recalled in the third immediate verbal trial are also recalled after a delay. In early childhood, the DS group only recalled on average 54% of the items recalled in WM trials, whereas the TD group recalled 76%. However, these results do not support the hypothesis of equally developing decay in verbal memory between groups.

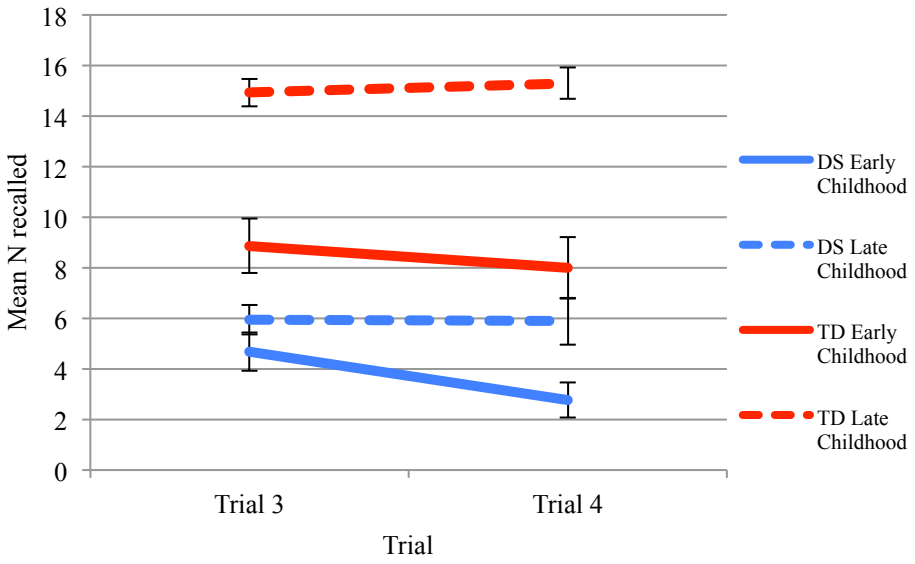

Figure 4.10 Mean N recalled in the final immediate verbal trial (trial 3) and the delayed verbal trial (trial 4). Error bars represent +/- 1 SE

4.3.8 Correlations between learning and decay in verbal memory, WM, LTM and CA, verbal and non-verbal scores and verbal fluency

To assess if the behaviours in the immediate and delayed verbal memory tasks were associated with raw and MA measures of other verbal assessments, correlation analyses were carried out. The measures of learning and forgetting, in other words, change across the three immediate verbal trials and decay between the third and fourth trials, were included, as well as WM and LTM. WM was the average N recalled in the first three trials, whereas LTM was the N recalled in the delayed trial. These were correlated with CA, digit span MA, and raw verbal fluency outcomes, as well as verbal and non-verbal outcomes, as shown in Table 4.3.

In the DS group, learning did not correlate with any measures. However, verbal decay measure correlated with CA, verbal and non-verbal measures. WM correlated with all measures excepting non-verbal raw measures which was merely

borderline significant, and LTM correlated with all excepting verbal fluency, suggesting that that verbal LTM is not associated with a frontal cognitive measure of verbal ability.

In the TD group the learning variable did not correlate with any experimental measure or with CA, whereas the measures of decay, WM and LTM significantly correlated with all experimental measures and CA. This indicates that encoding and retrieval of verbal LTM data improved with increasing CA, verbal WM and language abilities in the TD population.

Table 4.3 Correlation coefficients, significance and N's for learning and decay and CA, digit span MA, raw verbal fluency, non-verbal and verbal MA equivalents split between DS and TD groups. CA and all MA in months

Group	Measure	Statistic	CA	Digit Span MA	Verbal Fluency	Non-Verbal measure	Verbal score
DS	Learning	Pearson Correlation	0.237	-0.086	0.168	0.332	0.215
		Sig. (2-tailed)	0.215	0.689	0.392	0.109	0.263
		N	29	24	28	26	29
	Decay	Pearson Correlation	0.473**	0.331	-0.057	0.413**	0.389*
		Sig. (2-tailed)	0.01	0.107	0.772	0.032	0.037
		N	29	25	28	27	29
	WM	Pearson Correlation	0.414*	0.572**	0.583**	0.375	0.474**
		Sig. (2-tailed)	0.021	0.003	0.001	0.054	0.007
		N	31	25	30	27	31
	LTM	Pearson Correlation	0.503**	0.418*	0.312	0.709**	0.492**

		Sig. (2-tailed)	0.004	0.038	0.094	<0.001	0.005
		N	31	25	30	27	31
TD	Learning	Pearson Correlation	-0.197	-0.193	-0.072	-0.251	0.008
		Sig. (2-tailed)	0.28	0.29	0.694	0.166	0.965
		N	32	32	32	32	32
	Decay	Pearson Correlation	0.474**	0.532**	0.536**	0.499**	0.442*
		Sig. (2-tailed)	0.007	0.002	0.002	0.004	0.013
		N	31	31	31	31	31
	WM	Pearson Correlation	0.774**	0.505**	0.636**	0.486**	0.690**
		Sig. (2-tailed)	<0.001	0.003	<0.001	0.005	<0.001
		N	32	32	32	32	32
	LTM	Pearson Correlation	0.661**	0.568**	0.656**	0.464**	0.602**
		Sig. (2-tailed)	<0.001	0.001	<0.001	0.008	<0.001
		N	32	32	32	32	32

* $p<0.05$, ** $p<0.001$

4.3.9 Spatial distribution and verbal recall

Due to the novel format of our presentation of verbal data, as a grid of images rather than an auditorily presented list, the relationship between the spatial locations of an item and how well it was recalled was analysed. Therefore, the recall of each item was summed within groups over immediate and delayed trials, and correlated with our rating of "edge-ness". This was a simple system created by designating corner items the most "edge" with a value of 2, all other edge items given the value of 1, and all central items were given the value of 0. A correlation between how many times the object was recalled in the WM and LTM trials, and the objects' edge-ness was carried out within groups.

The edge-ness of the object significantly correlated with its immediate recall in the DS group ($r(60)=0.58$, $p<0.001$), but there was not a significant correlation in the TD group ($r(60)=0.12$, $p=0.344$). Therefore, the DS group had significantly better immediate recall of items with a higher edge-ness rating than those in the middle of the grid, whereas the TD group did not display preferential recall for verbal WM information. In the delayed trial the DS group had borderline significance ($r(20)=0.44$, $p=0.051$) whereas the TD group were still non-significantly correlated ($r(20)=0.23$, $p=0.332$).

4.4 Discussion

Our initial hypothesis that the DS group would be impaired on verbal WM and LTM compared to the CA-matched TD group was supported by the results; large effect sizes were seen in WM and medium effect sizes in LTM. In addition to this, delayed recall of mid-list values, a more specific measure of LTM that precludes primacy or recency effects, was also significantly impaired in the DS group compared to the TD group. The development of verbal WM was significantly

impaired in the DS group, results that did not support the hypothesis, although the effect size was small. The development of verbal LTM was not significantly different between DS and TD individuals over childhood, supporting the hypothesis and illustrating uneven development of memory systems.

It was hypothesised that the rates of learning and forgetting in the DS group would be comparable to the TD group both as a whole, and across development. There was statistical evidence for a significant difference in rates of learning between groups, with small effect. However, there was no evidence for the rates of learning over immediate trials being significantly different across childhood between groups. The implication of this finding is that the ability to learn did not develop significantly differently between DS and TD individuals across childhood. This has consequences for real-life environments such as teaching, for children with DS. If the development of rates of learning are not significantly different, then it is possible children with DS are capable of achieving greater levels of competence than currently observed, if they were given a higher number of exposures to the information. The effect of age was still significant in this analysis, indicating that increased CA increased verbal WM capacity in both DS and TD groups, although the effect size was again small. In reference to the previous literature, participants with DS showed MA-appropriate rates of learning of verbal WM, this result shows that learning is not CA-appropriate (Carlesimo et al., 1997).

Comparing the loss of information across delay, there was no significant three-way interaction of trial by group and age-group, meaning the change in decay over development was not significantly different between groups. However, the age-group by group interaction was significant, meaning overall decay was significantly different between groups, which does not support the hypothesis that

rates of decay would be comparable between DS and TD groups across development, although the effect size was small. There was a significant effect of age, with late childhood groups experiencing less decay than early childhood groups, indicating that CA improves LTM encoding and retrieval of verbal memory, which was similar between groups with a medium effect size. This behaviour had also been shown to be MA-appropriate in previous literature, suggesting both learning and forgetting of verbal WM are MA but not CA appropriate in the DS population (Carlesimo et al., 1997). Overall, the hypothesis that the DS group as a whole would not be impaired at learning and decay of verbal information was not supported by the results, however both behaviours improved at comparable rates across childhood between groups.

The development of recency was hypothesised to be non-significantly different from the TD group, whereas primacy was hypothesised to not develop (Carlesimo et al., 1997; Jarrold et al., 2000; Vicari, Marotta, et al., 2004). The results are discussed in terms of WM and then LTM behaviours. In immediate trials of WM the results supported the hypothesis. In LTM the relationship between development and memory was different. Primacy and recency both appeared to improve across age at comparable rates in the TD and DS groups, whereas the development of mid-list recall was significantly different between groups; although the effect size was small. As mid-list item recall is thought to be the more genuine measure of LTM, it can be concluded that LTM and its development are significantly impaired in the DS population compared to TD groups (Hurlstone et al., 2014). However, although overall recall was impaired in DS compared to TD groups, the rates of development of primacy and recency effects were not significantly different between groups. Thus, in LTM, both effects improved with CA in the DS population.

This contradicts the hypothesis regarding primacy effects, but supports the hypothesis regarding comparable development of recency.

Previous research utilising immediate primacy assessments have shown impairments in adolescent DS recall (Carlesimo et al., 1997; Vicari, Marotta, et al., 2004). This study advances these findings by showing that the development of primacy is not comparable to TD development in WM, but in LTM the two groups improved at comparable rates, despite the overall impairment in verbal recall in the DS group. The literature also showed that recency effects were comparable to MA-matched TD groups (Jarrold et al., 2000). This study advances these findings by demonstrating that recency effects were impaired overall but developed comparably to CA-matched TD individuals in both WM and LTM storage methods.

It was also hypothesised that there would be a significant correlation between verbal WM and LTM and measures of language or verbal processing skills: digit span and verbal fluency. In the DS group verbal fluency and digit span MA did not correlate with either learning or decay of verbal information, showing the cognitive flexibility of language in the DS group was not associated with verbal encoding and retrieval abilities in either immediate or delayed assessments. Learning correlated with no measures, suggesting it was not developing in-line with CA, non-verbal scores or other verbal measures. Decay correlated with CA, nonverbal measures and verbal score. WM and LTM variables significantly correlated with all measures, with the exception of WM and non-verbal raw scores and LTM and verbal fluency. This agrees with previous findings that participants with DS were less likely to access LTM when carrying out verbal cognitive flexibility or memory tasks (Grieco, Pulsifer, Seligsohn, Skotko, & Schwartz, 2015). This also supports previous findings of associations between verbal fluency, digit span, and

verbal WM abilities in the DS population (Duarte et al., 2011; Stavroussi et al., 2016). The results advance the current understanding of cognitive development in DS by providing support that digit span and verbal fluency development were associated with verbal LTM abilities also.

In the TD group learning did not correlate with any measures, showing that the lack of correlations in the DS group does not necessarily indicate an atypically developing system. All other measure significantly correlated, showing the synchronous improvement in abilities associated with TD individuals. Overall, these findings suggest that the absence of correlations between verbal fluency, LTM and decay, and digit span and decay in the DS group were deviations from typical relationships between these variables.

Due to the novel method of presentation of verbal data to a population with DS, features of the recall observed were investigated. Usual assessments of verbal recall in TD and DS groups involve list presentation of digits or words, or sentence repetition. In this task items were presented in a grid of 4 x 5 images. Although it could be presumed that this was a visual task, assessing recall verbally ensured the use of verbal memory. In the DS group the recall of items in the immediate verbal trials significantly correlated with the spatial location of the item in the grid. Objects in the corners were most frequently recalled, followed by other edge items, and then by the central items, which were least well recalled. This implies that individuals with DS between the ages of 4 and 14 years use spatial processing to encode stimuli that are presented verbally and visually simultaneously, or rely on different scan paths to TD individuals of the same CA. In other words, they preferentially encode stimuli in spatial positions that are more salient and accessible, than stimuli that are in less unique positions, and this benefits their

verbal WM performance. This agrees with some previous research showing that more distinctive stimuli are better recalled, even in mixed presentation of data (Hulme et al., 2004).

In LTM, although the correlation was no longer significant, it was borderline significant, suggesting that this spatial processing preference in data encoding transfers from WM to LTM. In the TD group the correlations between recall of the item and the edge-ness of the item were non-significant in both WM and LTM assessments. Therefore, either the TD participants did not systematically utilise spatial processing to encode information presented both verbally and visually, or their memory span was large enough to not preferentially recall items based on spatial location. It is possible that, due to the structured presentation of the data, even younger CA TD individuals were benefitting from chunking the data, meaning the location of items did not preferentially affect their likelihood of being recalled (Cowan, 2010; Farrell, 2012; Towse et al., 1999). The implications of this finding for the DS population include the classroom, where presentation of information should be kept spatially distinct, and not in a crowded or clustered spatial environment.

Limitations of this study include that, due to the verbal nature of the task, 40% of the early childhood DS group could not be included in the analysis, meaning that this group is underrepresented. There is a gap in the literature examining younger individuals with DS, providing many opportunities for future possible research. For example, investigating the PSE and WLE in verbal WM and LTM in early development. Although increasing the cognitive load impairs verbal memory in people with DS, it would also be interesting to investigate the effect of articulatory suppression on the U-shaped curve of verbal memory, and on verbal memory for different presentation formats such as visual and auditory. The effect of

rehearsal, or specifically the type of rehearsal undergone, is thought to play a genuine role in converting WM to LTM (Craik & Watkins, 1973; Thaler et al., 2013). Research into the type of rehearsal and memory encoding mechanisms used by participants with DS over development would also prove beneficial in tailoring teaching methods. This could be investigated by providing more semantically meaningful stimuli in order to assess the difference between this and recall of unrelated items.

It would also be interesting to investigate the effect of word frequency on recall. Studies have shown that participants with DS rely less on their LTM storage of information, and access LTM less in memory tasks (Carlesimo et al., 1997). Therefore, individuals with DS may benefit less from the word frequency effect or previous vocabulary abilities than TD participants. Therefore, a study with words that are matched on frequency, or comparing recall for grids of more and less frequent words, could further illustrate mechanisms relied upon to encode information in both verbal WM and LTM (Hulme et al., 1997; Majerus & Linden, 2003).

Overall, verbal LTM development was more comparable to CA-matched TD individuals than verbal WM development. However, verbal WM abilities developed in line with all verbal MA and equivalent measures, as well as CA, whereas LTM did not develop with verbal fluency abilities, suggesting the development of verbal WM abilities was more in-line with within-domain cognitive development than verbal LTM abilities.

Chapter 5 Visuospatial Working Memory and Long-Term Memory

5.1 Introduction

In this section, the definition of visuospatial memory and theories behind different visuospatial memory functions and features are discussed. Features of visuospatial WM and LTM in TD individuals are described. The literature on visuospatial WM and LTM in the DS population is reviewed, before discussing the current study. Much of the necessary information pertaining to visuospatial memory function and findings have already been discussed in Chapter 3 Visual and Visuospatial Short-Term Memory, and thus will only be briefly reviewed herein.

5.1.1 Visuospatial memory

Visuospatial memory is the ability to acquire, retain and recall visually and spatially perceived data. This memory system can encode multiple data formats including objects as unitary perceptions, spatial perceptions of a scene as a single unit, or the relationships between objects and their location. Visuospatial memory is a more basic domain than verbal memory, as it does not require language to encode, manipulate or recall data. Therefore, visuospatial methods of memory acquisition are available prior to language-based memory acquisition (Palmer, 2000). Evidence from specific interference effects has shown that there are separate visual and spatial WM systems (Farmer et al., 1986; Klauer & Zhao, 2004). The dissociable nature of visual and spatial abilities have also been demonstrated in case studies of individuals who were specifically impaired in one but not the other ability (Farah et al., 1988; Levine, Warach, & Farah, 1985; Luzzatti et al., 1998). This does not imply that the two are in no way associated or related; it simply demonstrates that, to a degree, they are capable of acting alone. This is supported

by the finding that interfering with either memory format, and thus impairing its function, also negatively affects the performance of the other memory format, showing there is some cross talk or reciprocity, potentially occurring through a higher systemic component, such as the central executive (Klauer & Zhao, 2004; Logie & Marchetti, 1991).

Visuospatial memory relies on visual information such as colour, size and shape, as well as spatial information such as organisation and dimensions. However, visuospatial memory or processing can also be relied upon when the input is verbal. For example, when text describes a route, or a scenic display, visuospatial memory is used in processing that verbally presented information (De Beni et al., 2005). This ability does not require sight; evidence has shown that although congenitally blind persons are impaired in visuospatial memory tasks compared to TD individuals, they are still capable of carrying out both visual and spatial processing tasks (Vecchi, 1998). Articulatory suppression impaired performance on visuospatial tasks equally in the blind and sighted groups, indicating that both groups comparably rely on verbal encoding in these assessments (Vecchi, 1998). Further to this, altering the level of cognitive control did not significantly affect the performance of the TD group, whereas the blind group were significantly impaired at higher levels of control compared to lower levels (Vecchi, 1998). Therefore, the blind group may have less available cognitive function flexibility during these tasks, meaning that increasing the cognitive control required impaired ability outcomes. The TD group utilised relatively less cognitive storage or manipulation capacity when carrying out the same tasks, meaning that increasing the cognitive load of the task did not affect their performance. These findings illustrate the ways in which visual, spatial and visuospatial memory

function can incorporate verbal information, and that cognitive control does not alter the abilities of TD participants, but may have an effect on those with less flexible cognitive faculties.

5.1.2 Theories of visuospatial memory

As previously outlined in Chapter 3, there are multiple theories of visuospatial memory function. For the sake of this study the function of visuospatial memory will be discussed in reference to the Baddeley model, which is now briefly reviewed (Baddeley, 1986). According to this theory, visuospatial WM is reliant on the visuospatial sketchpad, which is responsible for the maintenance and manipulation of visual and spatial information. It is divided into the inner eye, or visual cache, and the inner scribe (Logie, 1995; Logie & Pearson, 1997). The visual cache is a short-term, spatially limited feature, responsible for visual information such as colour, size, and shape (Logie & Pearson, 1997). The inner scribe is a more complex function, mainly responsible for manipulation of spatial information, such as dimensions and relative distances (Logie & Pearson, 1997). It has been hypothesised that the scribe is also responsible for translating information into a format that can be stored in the sketchpad, in the same way the sub-vocal articulatory loop does for verbal data (Gyselinck, Cornoldi, Dubois, De Beni, & Ehrlich, 2002; Logie, 2005).

Visual perception of pictures, as well as reading or hearing descriptions of spatial patterns or environments, automatically utilises visuospatial memory faculties (Denis, 1996). Thus, in addition to visually encoded visuospatial information, the sketchpad is also used for visual construction of data from auditory or written information. There is some evidence that recall of data from multiple inputs is better than recall for a single data format. For example, recall of data from

illustrated texts, which require reading and also have supplemental visual information, is better than recall for text without images (Gyselinck, Ehrlich, Cornoldi, De Beni, & Dubois, 2001). This implies that encoding data with multiple systems strengthens the storage of information, and increases the likelihood of it being retrieved at a later date. However, it is possible this is merely caused by verbal labels being applied to the images on top of the verbal information that is read, making this a purely verbal task. Spatial tapping interference impaired illustrated text, but not plain text recall, whereas verbal interference impaired recall of both tasks (Gyselinck et al., 2002). This interference comparison confirms that it is visuospatial WM, rather than verbal WM that is responsible for the improved recall of dual visually and verbally presented data. This finding supports the theory that memories are stored more securely if encoded by multiple systems, suggesting that to improve the likelihood of recall, multiple formats of presentation could be used simultaneously.

Some of the terminologies involved in this literature that lead to potential confusion, and the definitions of terms used herein are now discussed. The 'what' and 'where' of memory processing are structurally separate, as shown by functional neuroimaging studies (Courtney et al., 1996; E. Smith et al., 1996). However, location memory is frequently referred to as a spatial ability of visuospatial memory, but if it is the location of a specific object that is being assessed then visual processing will also be required to recall the object and its location. In the literature, matrix memory is referred to as a measure of visual memory (Cowan, Naveh-Benjamin, Kilb, & Saults, 2006; Della Sala et al., 1999). When reconstructing a matrix the participants have to recall locations of black and white squares, giving this 'visual' task a spatial component. Thus, although it can be attempted, it is

almost impossible to be certain that any paradigm is purely assessing one sub-function of visuospatial memory. For this reason it may be preferable to refer to a study as assessing 'mainly visual' or 'mainly spatial' abilities, rather than claiming to be able to fully dissociate the two skills.

Visuospatial data can be presented simultaneously or sequentially, these are also referred to as static and dynamic presentations respectively (Pickering et al., 2001). However, these terminologies further confuse the definitions of visual and spatial processing in the study of this memory domain. If a blank matrix is presented and the black squares are then presented sequentially, then this 'visual' task takes on a spatial aspect, as the sequential presentation of black squares is analogous to a pathway or route construct in the brain. There is no discernible difference between sequential matrix presentation and the Corsi block task, a quintessentially spatial assessment (L. Jaap Kappelle, 2000). Alternatively, if a spatial task, such as a virtual Corsi block assessment, is presented simultaneously then it loses a degree of the spatial nature of the task and becomes more visual. Therefore, in visuospatial assessments, if authors refer to their method of presentation as either simultaneous or sequential, then it is important for them to verify the claims that they are assessing a particular aspect of memory. This is seen in the Pickering et al., (2001) paper where the relationships between static and dynamic presentations of visual and spatial tasks were examined. TD participants performed better at static than dynamic tasks overall. However, the performance levels of both static and dynamic spatial tasks, and the dynamic visual task were not significantly different, whereas the performance in the static visual task was significantly better than all three (Pickering et al., 2001). The finding that the dynamic visual performance was not significantly different from any spatial

assessments implies that the dynamic nature of the task may make it more comparable to a spatial task than a visual task. However, on these lines of reasoning it might be expected that the static spatial performance would be more comparable to the visual assessment, which it was not. Therefore, it is possible that visual memory is significantly better than spatial memory, if stimuli are presented statically. Spatial memory was not significantly affected by the mode of stimuli presentation, implying that although the overall ability level of spatial memory was lower than visual memory, it was more robust to potential influences.

Further to the divide into visual and spatial processing of memory, there also appears to be a divide between active and passive visuospatial memory recall skills, as demonstrated by individuals with two different developmental disorders who have opposite ability profiles, i.e. some individuals proficient at recognition and impaired for recall, some proficient at recall and impaired for recognition (Cornoldi, Rigoni, Venneri, & Vecchi, 2000). Active and passive retrieval of memories are referring to recall and recognition, respectively. Recall, or active retrieval of memory, is thought to require greater control, meaning that some individuals are impaired on a lower level control task but not impaired in tasks that require higher control, which is an unexpected result (Cornoldi et al., 2000). This finding is evidence that the degree of cognitive control an individual is capable of is not linearly correlated with behavioural outcomes. In other words, although an individual may be capable of high level cognitive control tasks, if the passive-processing sub-system is malfunctioning, the individual will not be able to carry out the low-control cognitive tasks of recognition. Therefore, separable visuospatial processes are responsible for recognition and recall. It is possible that both visual and spatial memory formats are broken into simple stores that contribute to

recognition, and more complex manipulation or rehearsal components involved in recall.

Visuospatial memory is subject to a VSE, seen in younger children where recall is specifically impaired for visually similar, as opposed to more distinct stimuli (Hitch, Halliday, Schaafstal, & Schraagen, 1988). This effect is more prevalent in early childhood due to an increased reliance on the visuospatial recall system, whereas in later childhood verbal memory encoding methods are used in concert with visuospatial memory, which reduces the VSE (Palmer, 2000). There is also a WLE associated with verbally labelling stimuli, due to the limited capacity of the phonological loop. Recall for visual stimuli with longer names is increasingly impaired between the ages of 5 and 10 years (Hitch et al., 1988). This implies that verbal labelling of visual stimuli is used together with visuospatial memory encoding to some degree from early childhood, meaning the length of the name of the item may contribute to the successful function of verbal memory.

Generalised interference is introduced in visuospatial tasks by requesting the participant to perform a sequence of taps. However, specific visual or spatial interference can also be used to demonstrate the degree of independence of the systems (Baddeley & Lieberman, 1980). An example of a specifically visual interference task is instructing the participant to discern between the brightness of two lights. An example of a specifically spatial interference task is instructing the participant to follow a sound presented on four sides via directional buttons.

Although visuospatial memory can encode data from multiple input sources, the majority of visuospatial assessments present visual, rather than auditory or sensory data, especially when working with children. Spatial memory is typically assessed using the Corsi block test (L. Jaap Kappelle, 2000). This involves a board

with blocks randomly affixed to the surface. Thus, a 2D spatial array of random targets are presented, this can also be done virtually using a tablet. The experimenter taps a sequence on the blocks and the participant is instructed to repeat the sequence. The spatial memory capacity is determined by increasing the span of the sequence until the participant fails to recall sequence of a certain length correctly. Visual memory is assessed with memory for object paradigms. The visual memory capacity is determined by increasing the number of objects presented until the participant fails to recall them all. To avoid or reduce the reliance on verbal memory, random, non-nameable colours or shapes can be presented as stimuli, and the test trial can present the target item with distractors.

5.1.3 Visuospatial memory in typical development

The separate functions of visual and spatial processing are present by 4 years of age in typical development (Alloway et al., 2006). In line with the emergence of these skills, TD individuals preferentially encode memory stimuli in a visuospatial format from the ages of 4 to 7 years (Hitch et al., 1988; Palmer, 2000). There is an age-related increase in visuospatial memory span from age 4 years to adolescence (Gathercole, Pickering, Ambridge, & Wearing, 2004). This is suggested to be due to a development in processing skills, which then require less cognitive energy, enabling this energy to be used to maximise storage capacities from middle childhood onwards (Case et al., 1982).

Studies have shown spatial sequential memory abilities, assessed by Corsi blocks, increase significantly from the age of 7 to 10, and continued to improve slightly until 15 years of age (Isaacs & Vargha-Khadem, 1989). Interestingly these authors also assessed backwards Corsi span in TD individuals. This was not significantly poorer than forwards span, implying that order is less important in

visuospatial processing than verbal WM, where significant lower accuracy is seen in backwards processing tasks. Therefore, within the age ranges included in this thesis, the expectation is that the early childhood group may significantly improve in sequential spatial abilities, but no significant changes should be seen in the late childhood group.

Between 5 and 12 years of age visual memory develops faster and performs better than spatial memory (Logie & Pearson, 1997; Pickering et al., 2001). However, follow up studies suggested that these findings were driven by the uneven outcomes of the assessments used. In other words, the visual tasks had a greater range of possible scores than spatial tasks, which had a lower ceiling (Gathercole et al., 2004). This highlights the importance of controlling for outcomes when comparing multiple tasks, perhaps by expressing the results as percentages or z-scores, rather than raw or standardised scores. Although this does not remove floor and ceiling effects, it does permit for comparisons between tasks that were originally too different to contrast. Corsi block is the most common assessment of spatial memory function. This skill dramatically improved between age 7 and 10 years, and then slowly improved until around 15 years of age, but only to small degrees (Isaacs & Vargha-Khadem, 1989).

When considering the development of static and dynamic presentations of visuospatial data, few studies have directly contrasted development of these skills. Results showed that statically presented visual abilities significantly improved between age 5, 8 and 10 years, and were significantly better at all time points than all other visuospatial memory skills (Pickering et al., 2001). Dynamic visual task skills also significantly improved, but only between 5 and 10 years of age, indicating a more shallow gradient of improvement (Pickering et al., 2001). At all ages the

static visual skills were significantly better than dynamic. At age 5 years, there was no significant difference between skills in dynamic or static presentations of spatial tasks, whereas at age 8 and 10 years static skills were significantly better than dynamic, and this difference increased across time (Pickering et al., 2001). Static and dynamic spatial skills significantly improved between each age-group (Pickering et al., 2001). Therefore, this study showed that in childhood, presenting visual information sequentially significantly impaired recall performance compared to static or simultaneous presentation. In early childhood temporal presentation of spatial data was irrelevant, but by aged 8 years static presentation was again better recalled than dynamic presentation.

The mode of presentation of stimuli is important to consider, as processing is different for visually and auditorily presented visuospatial tasks (Crottaz-Herbette, Anagnoson, & Menon, 2004). Auditorily presented visuospatial tasks include, for example, reconstructing an auditorily presented environment. Overall, the literature suggests that simultaneously presented visuospatial information is better recalled than sequentially presented information, and that dual presentation of data with both visual and spatial information increases the likelihood of recall (Gyselinck et al., 2001; Lecerf & de Ribaupierre, 2005).

Recency effects are found in visuospatial WM tests (Pickering et al., 1998). In early childhood, recency is more exaggerated in backward recall trials, but also occurs in forwards recall, whereas primacy is absent in either recall order. In later childhood primacy is strongly observed in forwards recall, and recency is still observed in both forms of recall (Hitch et al., 1988). Recency and primacy in visuospatial memory appear to be exaggerated when the last or first items are required to be recalled first, respectively. Therefore, in visuospatial memory there

seems to be preferential recall of the items that are assessed first, suggesting that information in the visuospatial store rapidly decays.

5.1.4 Visuospatial memory in Down syndrome

At low cognitive control levels visuospatial memory was not significantly impaired in individuals with DS compared to TD controls matched on Logical operations (Lanfranchi et al., 2004). However, at higher levels of cognitive control, manipulated by increasing the complexity of the task, e.g. forwards vs. backwards path recall, participants with DS were impaired compared to both CA- and MA-matched TD groups (Lanfranchi, Jerman, et al., 2009). Spatial memory appears to function better than visual WM in participants with DS, which is opposite to the pattern in TD individuals (N. R. Ellis et al., 1989). Indeed, research has shown that participants with DS can outperform BPVS or SBIS-matched TD participants in WM and LTM spatial tasks, and perform equally well on visual tasks that cannot be verbally labelled, but were delayed on tasks that can utilise verbal labelling (Laws, 2002; Vicari et al., 2005). These studies included participants with DS CA 7:05 to 29:07, MA 4:03-5:04, thus the MA of these participants was above the age when visuospatial WM domains would be developed in TD individuals. However, this does not mean that these domains are fully developed in this atypical population, and inferences about the developmental trajectories of these domains should be made with caution. The discrepancy between performances in tasks that could or could not be verbally labelled indicates a different degree of reliance on encoding mechanisms in groups with and without DS (Laws, 2002). Where the MA-matched TD group benefited from verbal labelling of visual stimuli, the DS group did not to the same degree (Laws, 2002).

Participants with DS appear less delayed in sequential spatial WM than simultaneous spatial WM abilities, another finding that is opposite to the TD population (Lanfranchi, Carretti, et al., 2009). Within simultaneously presented memory tasks, participants with DS age 9 to 18 years benefited less from patterned as opposed to random data than BPVS-matched TD individuals, this difference was not seen in sequential data presentation (Carretti et al., 2013). Between the ages of 10 and 18 years participants with DS had a reduced visual memory span if the stimuli could be verbally labelled than logical operations-matched TD group, and also displayed the VSE (Lanfranchi et al., 2014). The development of visuospatial memory skills over MA of 4:06 to 7:07 years, assessed by Stanford-Binet Abbreviated Battery (SBAB), was not significantly different to the TD rate of development (Carney, Henry, et al., 2013). The finding that the MA-matched TD group benefited from structured presentation of stimuli, whereas the group with DS did not, implies a higher order processing ability in TD individuals that recognises patterns and reduces the cognitive load required to encode data in this situation compared to that in randomly assorted patterns (Carretti et al., 2013). This ability appears to be under-developed or missing in participants with DS. Overall, the features that benefit TD visuospatial memory, patterns, verbal labelling and simultaneous presentation, do not benefit the DS population to the same degree.

A group of 25 individuals with DS between 7 and 18 years of age were compared to WISC or WAIS-matched and PPVT-matched TD groups on recall associated with verbal-visual or visuospatial-visual data (Duarte et al., 2011). Although adding a visual component increased recall abilities of the DS group to non-significantly different to the PPVT-matched TD group, only dual visuospatial presentation improved DS performance to non-significantly different to both

control groups (Duarte et al., 2011). Therefore, immediate recall of visuospatial data is comparable between DS, IQ based MA-matched and PPVT-matched TD participants (Duarte et al., 2011).

Although no studies have directly assessed loss of visuospatial information from immediate to delayed trials in the DS population, a study comparing visuospatial encoding of word lists indicated that decay of information was not significantly different between DS and RCPM-matched TD groups (Purser & Jarrold, 2005).

5.1.5 The current study

The aim of this study was to investigate the performance of individuals with DS in an assessment of visuospatial WM and LTM that has not been previously used in the literature. It was decided to capitalise upon the improved recall observed with simultaneous verbal, visual, and spatial presentation of data. Therefore, the BAS 2 immediate and delayed spatial memory assessment paradigm was used. This paradigm was also selected as it would allow a direct comparison between verbal and visuospatial memory development, see Chapter 4. The immediate trial was a measure of WM, and the delayed trial was a measure of LTM. The aim of the study was to assess recall abilities, and patterns within those abilities, over early and late childhood in the DS population. Due to the spatial nature of the task presentation and test, any relationship between successful recall of items and the spatial location of item was also investigated.

The presentation of this task is both simultaneous and sequential. The stimuli are presented simultaneously on a card, but the items are also verbally labelled sequentially by both the experimenter and the participant. Therefore, it cannot be hypothesised whether the impairment associated with simultaneously

presented stimuli will be observed in the DS group. Due to this unusual sequential nature of the visuospatial task, the effects of primacy, mid-list recall and recency are also analysed herein, to identify differences in behaviours between the two participant groups across time.

It was hypothesised that both WM and LTM in the DS group would be impaired compared to CA-matched TD individuals. Based on the work of Carney (2013), it was hypothesised that the development of visuospatial WM would not be significantly different. Although no previous work on the development of visuospatial LTM, it was also hypothesised that the development of LTM would not be significantly impaired. It was also hypothesised that the decay between immediate and delayed recall would not be significantly different between the DS and TD groups. There is little literature on the effects of primacy and recency in visuospatial recall in the DS population, thus these effects, and mid-list recall, were investigated without directional hypotheses relating to the phenomena.

All visuospatial WM and LTM recall outcomes were correlated with CA, non-verbal measures and visual WM MA derived from pattern construction and picture recognition tasks respectively, as well as verbal score derived from the BPVS. This was to examine the synchrony of development of these abilities in TD and DS groups over childhood.

5.2 Methods

5.2.1 Participants

Participants with and without DS were recruited as described in 2.2 Participants. Forty-three participants with DS were recruited between the ages of 4 and 14 years old. Thirty-two TD participants were recruited between the ages of 4 and 14 years. Nineteen participants with DS were excluded due to failure to attempt

or complete the immediate spatial task. Fourteen of the excluded participants with DS were in the early childhood group and the remaining five were in the late childhood group. Therefore, the groups consisted of 24 participants with DS and 32 TD participants, split into early and late childhood as shown in Table 5.2.

5.2.2 Procedure

Immediate and delayed visuospatial memory abilities were assessed using the BAS 2 components as described in 2.4.3.2.3 Immediate and delayed verbal and visuospatial recall. The participant was initially guided through the images and asked to verbally name each one. In the DS group the experimenter and the participant then went sequentially through the grid naming the images together. The participants were each tested on verbal recall of the items three times before the visuospatial assessment, meaning they were exposed to the grid three times, for an average of 3 minutes total in the DS group, and 2 minutes total in the TD group. Due to the sequential nature of this task, any individuals who could not complete a single verbal trial, or were non-verbal, were excluded from this task. Although this may seem counterintuitive, it was important in the testing protocol that none of the participants were discouraged by being unable to complete a task, therefore if they were unable to label the 20 items, the entire protocol of verbal and visuospatial memory assessment was skipped. Furthermore, as all the TD participants could name the items, if the participants with DS were unable to then it could impair their recall abilities for reasons other than visuospatial impairments.

The final component of the immediate recall involved providing 20 individual cards with the card components printed on, face-up before the participant and instructing them “These cards have the pictures on them, I want you to put them together so they look like the big picture you saw earlier. Try to

remember where each picture should go". The participants were also provided with a grid to obviate how the cards should be arranged, i.e. in a 4 x 5 grid. There was also a LTM assessment of visuospatial memory abilities identical to the immediate test following an interval of 15 to 25 minutes, but without any exposure to the pictures. The instructions were "Now I want you to try to remember where the pictures should go. Put these cards on the grid like you did before, to show where the pictures went". With younger, or less able, participants the instructions were simplified to "make it look the same as before", or a comparable instruction set with simplified vocabulary. In both the immediate and delayed trials the time limit for completing the grid was 4 minutes.

In addition to this two other components of the BAS 2 were administered, pattern construction and picture recognition, and the BPVS, as described in Chapter 2. The mean and standard deviation of the main assessments are outlined in Table 5.2.

5.2.3 Design

The study had both within- and between-group factors. Between groups are the participant groups of DS and TD and the age-groups of early and late childhood. Thus, the independent variables were group and age-group. Within groups were the changes in dependent variable outcomes over time. There are multiple dependent variables outlined in Table 5.1. The main dependent variable is referred to throughout as recall, meaning, the successful recall and placement of an item in the correct grid location.

PRIMACY= (ITEM 1 + ITEM 2 + ITEM 3)/3

MIDLIST= (ITEM 4 + ITEM 5 + ITEM 6 + ITEM 7 + ITEM 8 + ITEM 9 + ITEM 10 + ITEM 11 + ITEM 12 + ITEM 13 + ITEM 14 + ITEM 15 + ITEM 16 + ITEM 17)/14

RECENCY= (ITEM 18 + ITEM 19 + ITEM 20)/3

Table 5.1 The variables measured in this chapter and the assessment they are derived from, along with the minimum and maximum scores possible or achieved

Task	Variable	Minimum	Maximum
Immediate visuospatial	Recall	0	20
Delayed visuospatial	Recall	0	20
Immediate and delayed visuospatial (primacy, mid-list and recency)	Average N item in each block was recalled	0	1
BPVS	Verbal score (ceiling item –N of errors)	12	160
Pattern Construction	Raw score	1	62
Picture recognition	Age equivalent (months)	30	216

Note. *= No actual maximum, values represent maximum values achieved in the study

5.2.4 Analysis

The primacy, mid-list and recency effects for both immediate and delayed trials were calculated as above. Statistical analyses were carried out with IBM SPSS Statistics, Version 20 (IBM, 2011).

5.3 Results

5.3.1 Participants characterisation

The MA scores of the DS and TD groups in early and late childhood were compared with T-Tests, and are presented in Table 5.2. Unfortunately, in both early and late childhood, the TD MA scores for picture recognition were significantly higher than the mean CA of the groups. Therefore, these abilities are not representative of the general population. This means any direct comparison between the DS and TD groups on these measures are not informative. However, it is still possible that comparisons of trajectories of development between groups may still prove informative; therefore these scores are included only as correlational measures, in order to examine within-group features of development.

Table 5.2 The mean and standard deviation (SD) CA, verbal score (derived from BPVS) pattern construction raw score, and picture recognition MA of all participants included in this analysis, and the N included in each assessment

	Early Childhood		Late Childhood	
	DS	TD	DS	TD
Mean CA months (SD)	93.00 (10.53)	71.19 (18.25)	147.56 (24.38)	139.63 (18.90)
N	8	16	16	16
Mean Verbal score (SD)	58.63 (9.69)	88.38 (20.85)	69.50 (16.09)	143.69 (14.52)
N	8	16	16	16
Mean Pattern Construction raw (SD)	8.14 (6.54)	28.38 (14.87)	13.75 (7.71)	40 (13.35)
N	8	16	16	16
Mean Picture Recognition MA months (SD)	45.13 (16.17)	86.00 (20.87)	63.38 (20.63)	175.94 (39.95)
N	8	16	16	16

5.3.2 Overall difference in visuospatial memory

A two-way ANOVA was conducted to examine to effect of age and group on immediate and delayed visuospatial recall. The main effect of group was significant, with the DS group recalled significantly fewer items than the TD group ($F(1,52)=31.59$, $p<0.001$, $\eta_p^2=0.378$). There was no significant main effect of age

group ($F(1,52)=2.85$, $p=0.097$, $\eta_p^2=0.052$). There was not a significant interaction between group and age-group ($F(1,52)=2.574$, $p=0.115$, $\eta_p^2=0.047$), implying the change in recall over time was not significantly different between groups., as shown in Figure 5.1.

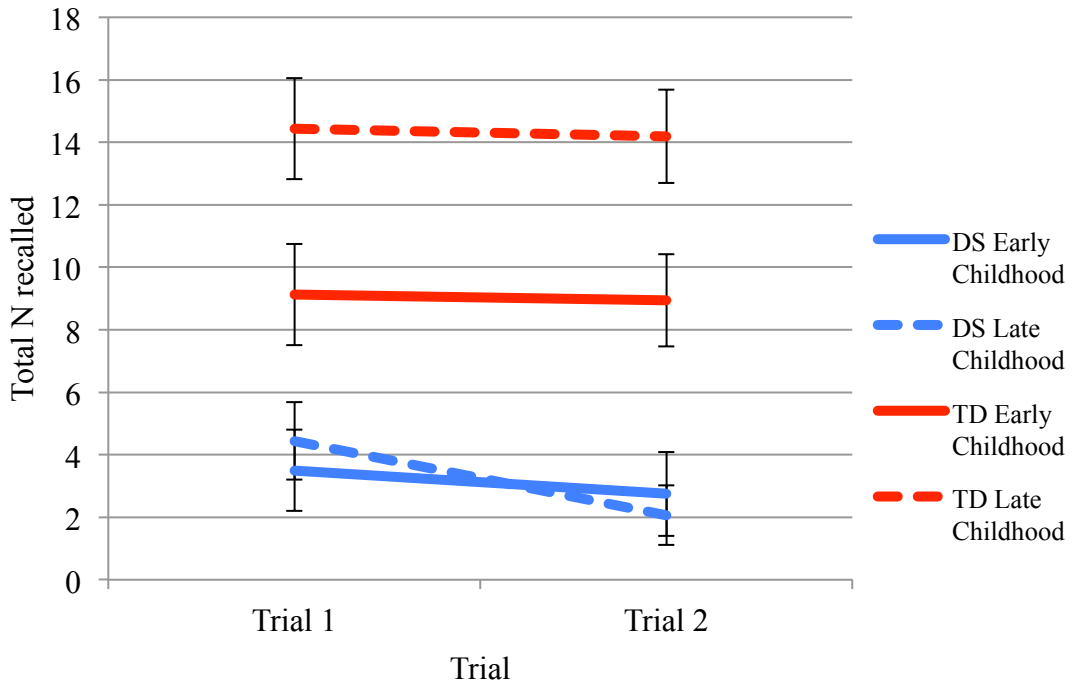

Figure 5.1 Overall visuospatial recall group means in immediate (trial 1) and delayed (trial 2) test trials in DS and TD groups over early and late childhood. Error bars represent +/- 1 SE

5.3.3 Differences in immediate visuospatial memory

A two-way ANOVA was conducted to examine the effect of age and group on immediate visuospatial recall. The main effect of group was significant, with impaired DS group performance ($F(1,52)=22.47$, $p<0.001$, $\eta_p^2=0.302$). There was no significant difference between recall in early and late childhood ($F(1,52)=3.33$, $p=0.074$, $\eta_p^2=0.06$). There was not a significant interaction between group and age-

group (F(1,52)=1.55, p=0.219, η_p^2=0.029), implying the change in visuospatial WM over time was not significantly different between groups, as shown in Figure 5.2.

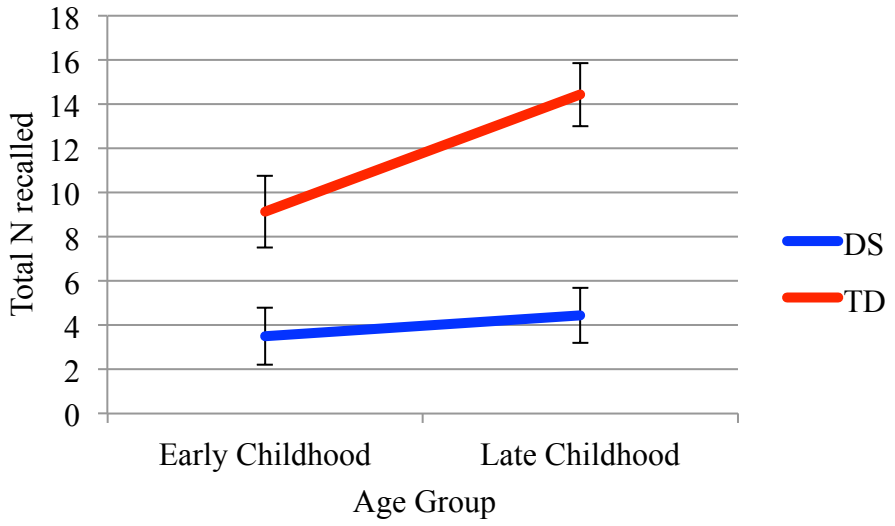

Figure 5.2 Mean N recalled in the immediate visuospatial trial in DS and TD groups over early and late childhood. Error bars represent +/- 1 SE

5.3.4 Primacy, mid-list and recency effects in the immediate visuospatial trial

A multivariate ANOVA was conducted to examine the effect of age and group on primacy, mid list recall, and recency effects. For primacy (F(1,52)=0.037, p=0.848, η_p^2=0.001), mid list (F(1,52)=2.822, p=0.099, η_p^2=0.051), and recency (F(1,52)=0.009, p=0.925, η_p^2= 0.000) recall the interaction effects of group and age group were not significant, , indicating these behaviours develop in a comparable manner in both groups. The effect of group was significant in all three measures (primacy: F(1,52)=16.44, p<0.001, η_p^2=0.240, mid list: F(1,52)=20.65, p<0.001, η_p^2=0.284, recency: F(1,52)=12.41, p=0.001, η_p^2=0.193). The main effect of age was not significant in primacy (F(1,52)=0.932, p=0.339, η_p^2=0.018), mid-list recall

($F(1,52)=3.20$, $p=0.079$, $\eta_p^2=0.058$), and recency ($F(1,52)=3.27$, $p=0.076$, $\eta_p^2=0.059$).

These results suggest the groups improved comparably across age in primacy WM, as shown in Figure 5.3, in mid-list WM, as shown in Figure 5.4, and in recency WM, as shown in Figure 5.5.

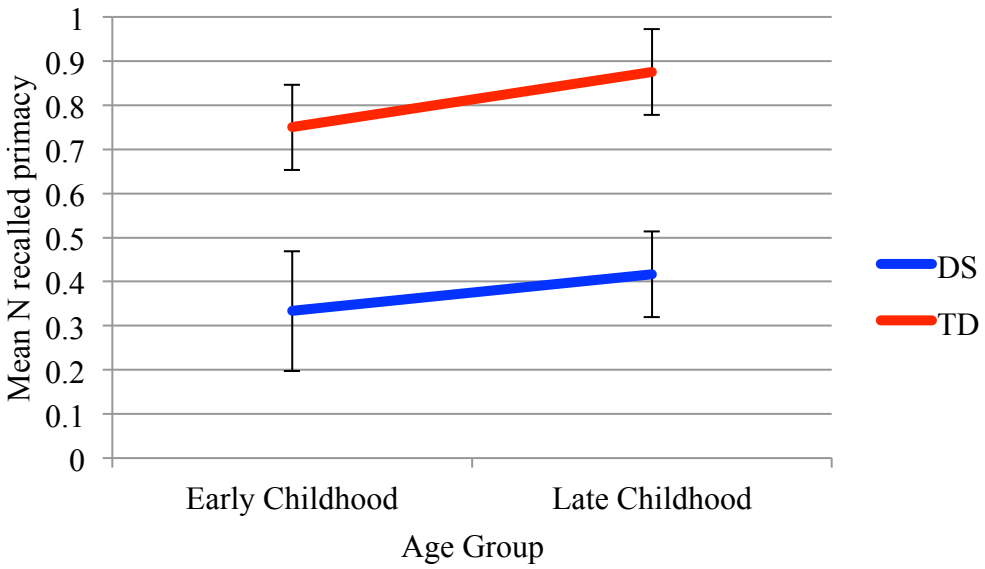

Figure 5.3 Mean N recalled of first 3 items in the immediate visuospatial trial. Error bars represent +/- 1 SE

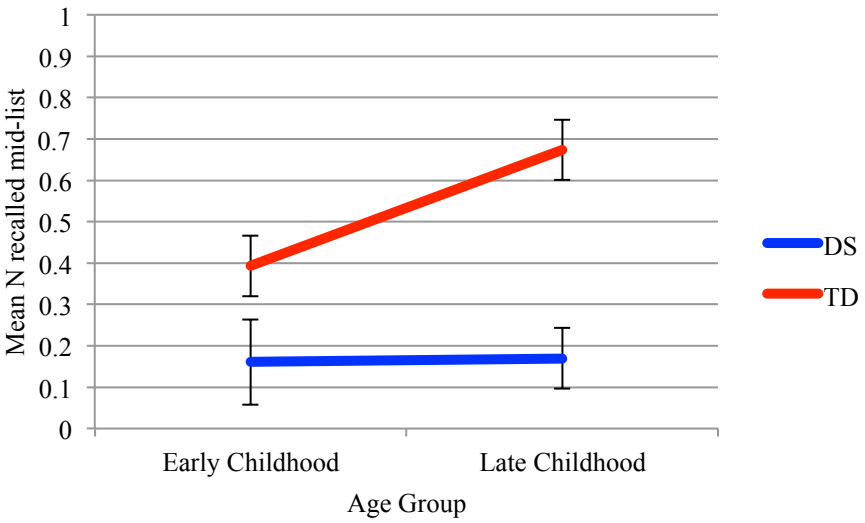

Figure 5.4 Mean N recalled of middle 14 items in the immediate visuospatial trial. Error bars represent +/- 1 SE

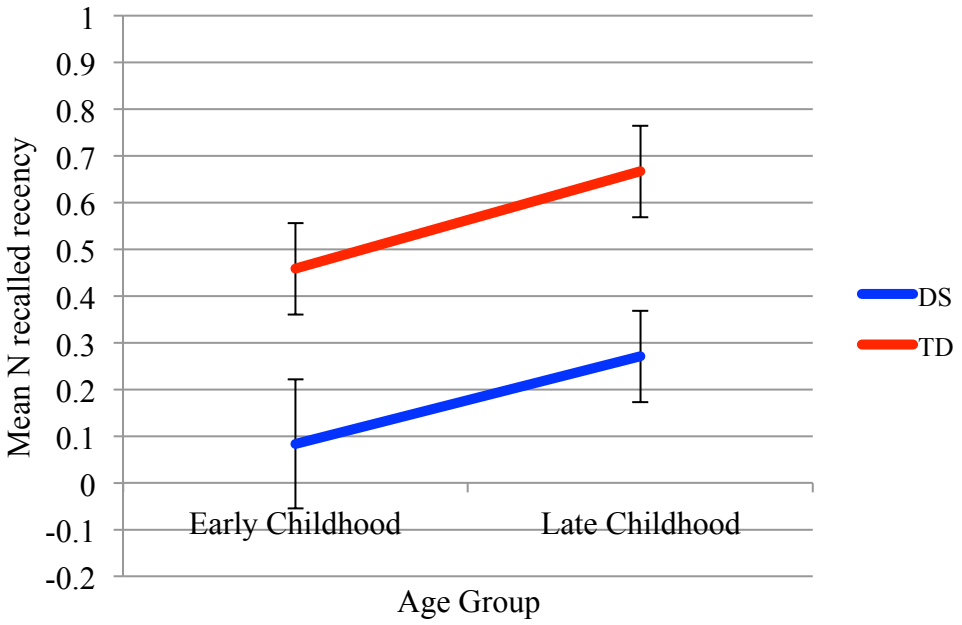

Figure 5.5 Mean N recalled of last 3 items in the immediate visuospatial trial. Error bars represent +/- 1 SE

5.3.5 Overall difference in the delayed visuospatial memory trial

A two-way ANOVA was conducted to examine the effect of age and group on delayed visuospatial recall, the DS group recalled significantly fewer items than the TD group ($F(1,52)=38.46$, $p<0.001$, $\eta_p^2=0.425$). There was no significant main effect of age between delayed recall ($F(1,52)=2.00$, $p=0.163$, $\eta_p^2=0.037$). There was not a significant interaction between group and age-group ($F(1,52)=3.58$, $p=0.064$, $\eta_p^2=0.064$), implying the change in visuospatial LTM over time was not significantly different between groups as shown in Figure 5.6.

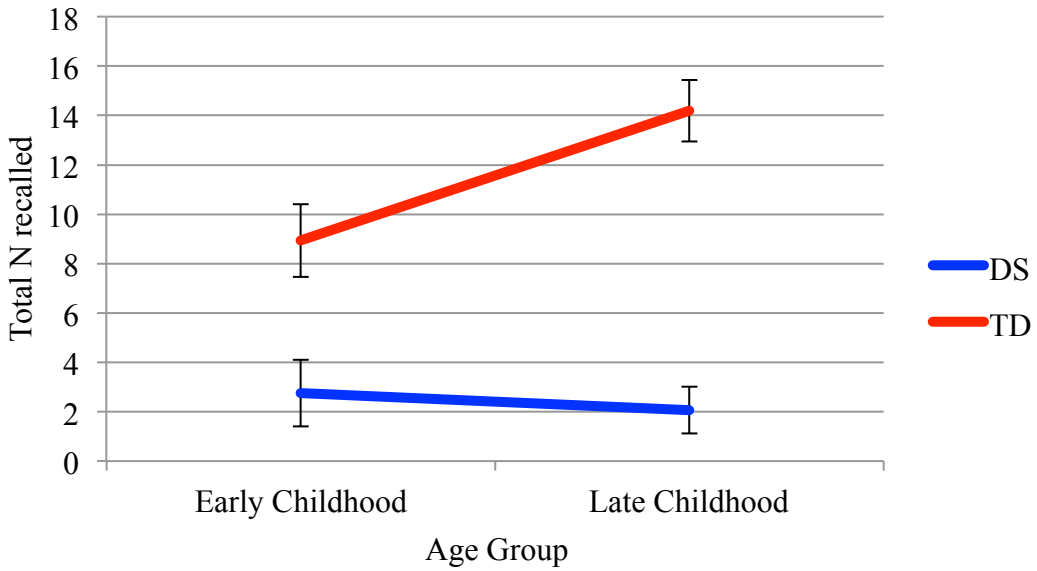

Figure 5.6 Mean N recalled in the delayed visuospatial trial in DS and TD groups over early and late childhood. Error bars represent +/- 1 SE

5.3.6 Primacy, mid-list and recency effects in the delayed visuospatial memory trial

A multivariate ANOVA was conducted to examine the effect of age and group on primacy, mid list recall, and recency effects. For primacy ($F(1,52)=2.24$, $p=0.140$, $\eta_p^2=0.041$), mid list ($F(1,52)=3.18$, $p=0.080$, $\eta_p^2=0.058$), and recency ($F(1,52)=2.39$, $p=0.128$, $\eta_p^2= 0.044$) recall the interaction effects of group and age group were not significant, , indicating these behaviours develop in a comparable manner in both groups. The effect of group was significant in all three measures (primacy: $F(1,52)=35.92$ $p<0.001$, $\eta_p^2=0.409$, mid list: $F(1,52)=32.02$, $p<0.001$, $\eta_p^2=0.381$, recency: $F(1,52)=21.51$, $p<0.001$, $\eta_p^2=0.293$). The main effect of age was not significant in primacy ($F(1,52)=0.046$, $p=0.831$, $\eta_p^2=0.001$), mid-list recall

($F(1,52)=2.36$, $p=0.130$, $\eta_p^2=0.043$), and recency ($F(1,52)=1.80$, $p=0.186$, $\eta_p^2=0.033$).

These results suggest the groups improved comparably across age in primacy WM, as shown in, as shown in Figure 5.7, in mid-list LTM, as shown in Figure 5.8, and in recency LTM, as shown in Figure 5.9.

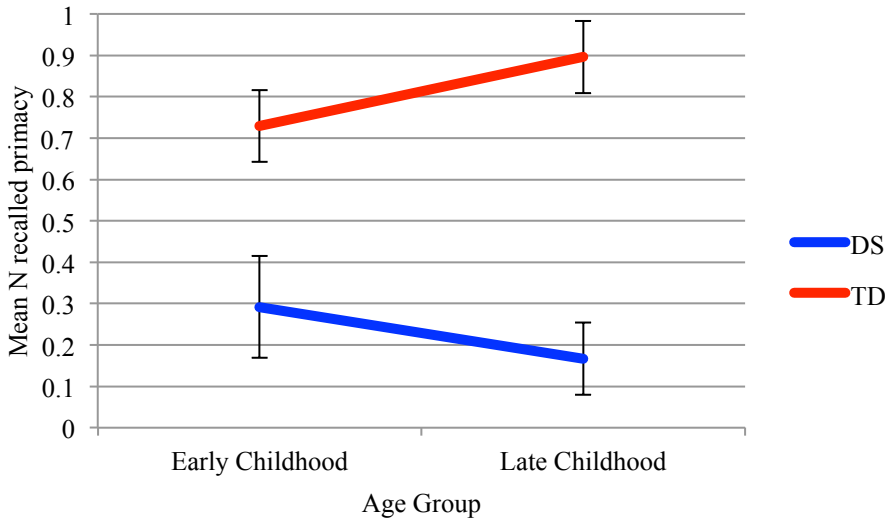

Figure 5.7 Mean N recalled of first 3 items in the delayed visuospatial trial. Error bars represent +/- 1 SE

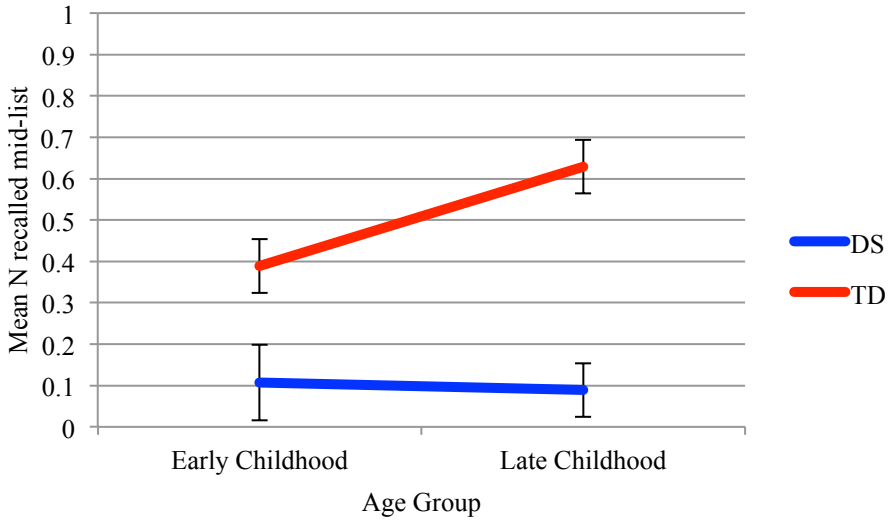

Figure 5.8 Mean N recalled of middle 14 items in the delayed visuospatial trial. Error bars represent +/- 1 SE

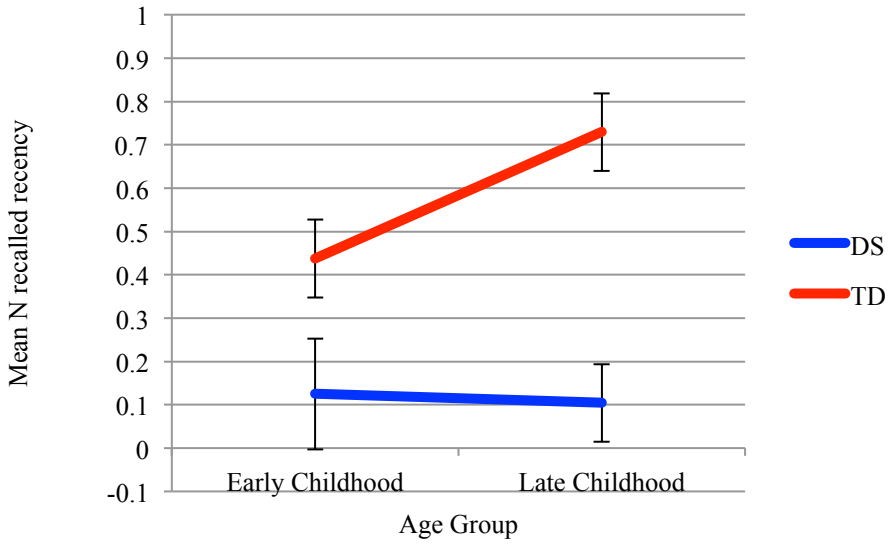

Figure 5.9 Mean N recalled of last 3 items in the delayed visuospatial trial. Error bars represent +/- 1 SE

5.3.7 Correlations between WM and LTM visuospatial memory and CA, visual, verbal and non-verbal measures

To assess if the behaviours in immediate and delayed visuospatial memory tasks were associated with other visuospatial measures, verbal and non-verbal correlation analyses were carried out, and are summarised in Table 5.3. The two visuospatial recall trials (WM and LTM) were correlated with CA, pattern construction raw and picture recognition MA, as well as verbal score.

In the DS group, the immediate trial did not correlate with CA, picture recognition MA equivalent or verbal score, but did significantly correlate with pattern construction raw scores. Therefore, pattern construction ability developed more synchronously with visuospatial WM abilities than picture recognition MA. The finding that CA did not correlate with visuospatial WM abilities implies that life experience does not contribute to these abilities. The lack of correlation between

visuospatial WM and picture recognition, a measure of visual WM, implies that visual and visuospatial WM did not develop in a correlated manner. The delayed trial as a measure of visuospatial LTM also did not correlate with CA, picture recognition MA or verbal score. Visuospatial LTM was significantly correlated with pattern construction raw scores. Overall, in the DS group, although neither visuospatial WM nor LTM abilities were significantly correlated with CA, visual measures of cognition, or the verbal MA equivalent, both did correlate with raw non-verbal scores.

In the TD group both visuospatial WM and LTM were significantly correlated with CA, pattern construction and picture recognition age equivalents, as well as verbal score outcomes. This indicates that in typical development, visuospatial WM and LTM develop in an associated manner with CA, non-verbal, verbal, and visual memory abilities.

Table 5.3 Correlation coefficients, significance and N's for WM and LTM visuospatial memory and CA, picture recognition MA, non-verbal raw (derived from pattern construction) and verbal score (derived from BPVS). CA and MA equivalents in months

Group	Measure	Statistic	CA	Picture Recognition MA	Non-verbal raw	Verbal score
DS	WM	Pearson Correlation	0.252	0.237	.622**	0.294
		Sig. (2-tailed)	0.235	0.265	0.002	0.163
		N	24	24	23	24
	LTM	Pearson Correlation	-0.066	-0.127	0.539**	-0.033
		Sig. (2-tailed)	0.759	0.553	0.008	0.877
		N	24	24	23	24
TD	WM	Pearson Correlation	.463**	.510**	.561**	.457**
		Sig. (2-tailed)	0.008	0.003	0.001	0.009
		N	32	32	32	32
	LTM	Pearson Correlation	.453**	.560**	.535**	.402*
		Sig. (2-tailed)	0.009	0.001	0.002	0.023
		N	32	32	32	32

* = <0.05, ** = <0.01

5.3.8 Spatial distribution and visuospatial recall

Due to the novel format of our presentation of visuospatial data, the relationship between the spatial locations of the stimulus and how well it was recalled was analysed. Therefore, the recall of each item was summed by group (DS

or TD) and correlated with our rating of "edge-ness", following the procedure in the previous chapter.

The edge-ness of the object significantly correlated with its immediate recall in the DS group ($r(20)=0.664$, $p=0.001$), and the TD group ($r(20)=0.594$, $p=0.006$). In the delayed trial the edge-ness of the object significantly correlated with recall in the DS group ($r(20)=0.650$, $p=0.002$) and the TD group ($r(20)=0.668$, $p=0.001$). Therefore, both groups had significantly better immediate and delayed recall of items with a higher edge-ness rating than those in the middle of the grid. This indicates that the scanning patterns or techniques used by the groups to store visuospatial information may not be significantly different.

5.4 Discussion

Our initial hypothesis that visuospatial memory would be impaired in the DS group compared to the TD group overall was supported by the results, with a medium effect size. This supports previous literature findings that showed that visuospatial WM and LTM were MA-appropriate at low control.

It was hypothesised that the change in visuospatial WM and LTM would not be significantly different between groups over development, based on the previous literature that found this relationship in MA-matched groups (Carney, Henry, et al., 2013; Purser & Jarrold, 2005). There was statistical support for this hypothesis, although the interaction of group and age-group was borderline significant in the development of visuospatial LTM abilities. In addition to this the effect size of group was larger in LTM than WM, further suggesting the difference between visuospatial abilities in the DS and TD groups is larger in delayed than immediate recall. Therefore, although there was statistical support for both WM and LTM developing comparably between the DS and TD groups, the development of LTM may be more

delayed than the development of WM in the DS group. This task had both sequential and simultaneous features, the sequential nature of the task may have benefitted the DS population (Lanfranchi, Carretti, et al., 2009). In addition to this, the stimuli were presented in two different data formats, visually and auditorily, which also improves recall abilities (Gyselinck et al., 2001). Therefore, these results are likely to represent the best of the DS groups' capabilities. However, the verbal labelling of the information may also exaggerate the discrepancy between the DS and TD groups, as TD individuals are capable of benefitting more greatly from dual verbal-visual data than participants with DS (Laws, 2002). These findings suggest possible future research, which is discussed later.

The finding that the development of visuospatial WM was CA appropriate adds to previous studies that showed MA-appropriate development of this ability between MA 4-7 years, as measured by the SBAB. The MA of the participants in this study, as calculated from the picture recognition task, was 4:09-5:02, a younger MA, but overall the results support both MA and CA appropriate development of visuospatial WM in participants with DS.

It was hypothesised that the rates of forgetting in the DS group would be comparable to the TD group. There was statistical support for this both as a whole, and across development. This adds to previous studies where rates of forgetting were MA-appropriate when matched on RCPM, by showing that forgetting or decay of visuospatial memory is both MA and CA appropriate (Purser & Jarrold, 2005).

It was also an aim of this study to investigate the effects of primacy, recency, and the recall of mid-list values. The recall of all items in both trials was significantly impaired in the DS group compared to the TD group, with effect sizes ranging from small to medium. The effect sizes were larger in visuospatial LTM

than WM, further suggesting that the difference between TD and DS groups increases across delay. However, the change with developmental time was also of interest, so the interactions between group and age-group were examined. In both the immediate and delayed trials none of the interactions were significant, implying that the change in primacy and recency effects, and mid-list recall, over age were not significantly different between the DS and TD groups. Previous studies on TD individuals showed most recently presented items were preferentially recalled (Hitch et al., 1988). No studies had examined the effect in the DS population. This means that, although the DS group recalled significantly fewer items overall than the TD group, the development of encoding mechanisms of visuospatial data was not significantly different in TD and DS groups in either WM or LTM assessments.

The relationship between WM and LTM recall of visuospatial information, and other visuospatial measures and CA were then examined. In the TD group, all variables significantly correlated with each other, indicating our grid measure of visuospatial recall in WM and LTM was associated with CA, non-verbal raw scores and a more specifically visual memory task MA, as well as verbal ability development. This is an indication of the even cognitive development associated with typical development, and agrees with the literature reports of improving skills over childhood (Gathercole et al., 2004; Isaacs & Vargha-Khadem, 1989; Pickering et al., 2001).

In the DS group the developmental profile was more uneven. The measure of visuospatial WM was associated with visuospatial processing raw score, but not visual MA, verbal score, or CA. This indicates that the development of visual picture recognition MA and visuospatial WM was not synchronous. Further to this, picture recognition is a recognition task, rather than a recall task, implying it should be an

easier task (Cornoldi et al., 2000). There was no correlation between visuospatial WM or LTM measures and verbal score, a measure of verbal ability development. This finding agrees with previous literature reporting a significant difference in verbal and visuospatial abilities in the DS population (Jarrold & Baddeley, 2001; Lanfranchi et al., 2004).

In the delayed trial, a measure of visuospatial LTM, the pattern construction raw score correlation also significant. CA and picture recognition were not significantly correlated with visuospatial LTM. Overall, visual recognition did not appear to develop in synchrony with visuospatial recall skills, whereas spatial skills associated with pattern construction, developed in synchrony with visuospatial WM, and also significantly with LTM abilities. This has two possible interpretations: the first being that the DS population are relying more on spatial than visual abilities to perform this task, which agrees with previous literature (N. R. Ellis et al., 1989). The second is that visual and spatial abilities develop at different speeds, and overall visuospatial processing relies more on spatial abilities than visual, perhaps due to a delay in spatial abilities that then becomes the rate-limiting factor. However, this does not agree with previous findings of better spatial than visual abilities in the DS population, making the former suggestion a more likely explanation (Vicari et al., 2005).

Both groups appeared to recall objects with a greater "edge-ness" rating better than those with lower edge-ness values. This indicates that visuospatial memory preferentially encoded items on the edge, and that recall was worse for items that were surrounded by other items, and that the mechanisms for encoding were not different between groups. Visual crowding could cause this result; meaning the separate identification and recall of these mid-grid items requires

greater cognitive control. This was seen in both WM and LTM assessments, indicating that the preferential item recall in WM visuospatial assessments was maintained over LTM encoding and retrieval, and that this process was similar in DS and TD groups. As in the verbal assessments, the implications of this are that items are better learned if they are more unique or distinct, suggesting over-crowding information in classrooms and learning materials is detrimental to the development of both typical and atypical visuospatial development.

The current study had some limitations. The most serious limitation was the small N of the early childhood DS group, having only 8 participants. This was due to the strict inclusion criteria of the assessment. More participants were able to complete the verbal assessment than the visuospatial assessments, as the fine motor skills required for the current task were too demanding for many of the younger participants with DS. Due to this limitation it is necessary to interpret findings with care. The strict exclusion criteria of all participants who failed the verbal task, and who were incapable of the motor manipulation required, means that this demographic are not truly representative of the DS population, where a wider range of abilities exists, and thus a wider range of outcomes would be expected. Although the complications of this task did prohibit many individuals from taking part, the multiple sources of data input and its comparability to verbal memory outcome measures, still made this task valid, but the data must be interpreted with care.

Another limitation of this study is the inability to assess the visual scanning paths of the participants, and associate these paths with successful recall of items. Although there was a significant correlation with the edge-ness rating of the items, it would also be interesting to associate this with looking time to each item and how

well the item was recalled. Based on the TD population finding that recall is better for items presented in multiple modalities, such as visually and auditorily, this method was applied herein (Lecerf & de Ribaupierre, 2005). However, the TD population also benefit more from verbally encoded information than the DS population (Laws, 2002). Therefore, it would be interesting to carry out multiple visuospatial recall assessment, where the data are presented with secondary, but non-verbal, information. For example, animals in a grid, presented with their associated calls, or vehicles and implements and their associated noises. Alternatively, visuospatial recall abilities and preferential spatial encoding of items that cannot be verbally labelled, i.e. nonsense objects, obscure colours, would also be interesting.

Overall, although visuospatial recall was delayed in the DS group compared to the CA-matched TD group, the trajectories of development of visuospatial WM and LTM abilities were not significantly different. This indicates that visuospatial WM and LTM skills develop comparably to the CA-matched TD population. Visuospatial WM abilities correlated with spatial but not visual tests of cognition in the DS population, whereas in the TD population these abilities were all correlated in both WM and LTM trials. Visuospatial LTM abilities did not significantly correlate with visual WM abilities but was related to visuospatial processing abilities. Neither measure correlated with CA in the DS population, suggesting this age-group did not undergo significant improvement in visuospatial WM or LTM abilities. Therefore, visuospatial processing abilities appeared to develop in synchrony with visuospatial WM and LTM abilities in the DS population. The lack of correlations between CA, visual MA and verbal score with visuospatial WM and LTM in the DS

population indicates the uneven development of these abilities compared to the TD population.

Chapter 6 Spatial-Auditory Associative Short-Term Memory and Long-Term Memory

6.1 Introduction

In this chapter, associative memory is defined and its role in human development is discussed. Features of associative memory and its development in the TD population are then examined, followed by a review of the literature addressing associative memory in the DS population. The current study is then described.

6.1.1 Associative memory

Human beings experience and interpret the world through five main senses. The majority of human memories are not composed of information from a single sense, but are complex multisensory, or multi-format, memories. This requires the integration of multiple sensory modalities as well as the individual's personal responses attached to the memory. These complex multifaceted memories are called associative memories, and referred to herein both in terms of multi-format and multi-domain reliant processes. The storage and retrieval of between-format associative memories are critically reliant on hippocampal function and other medial temporal lobe (MTL) structures (Burgess, Maguire, & O'Keefe, 2002; Mayes, Montaldi, & Migo, 2007). This is demonstrated by patients with hippocampal lesions, who are proficient at item recognition, recall, and within-format recall, but specifically impaired on between-format item binding, storage, and recall (Mayes et al., 2004; Vargha-Khadem, Gadian, & Watkins, 1997). Associative memory can integrate information including verbal, visuospatial, and temporal data. Patients with specific lesions or resections of brain tissues have provided evidence that

verbal, or narrative, memory function is more associated with the left MTL, whereas visuospatial memory function is more associated with the right MTL (Frisk & Milner, 1990; M. Lou Smith & Milner, 1981).

Visuospatial information can be integrated with information from any or all of the other senses; associations between visual and spatial information have been discussed in Chapter 3. The focus of this chapter is the integration of visuospatial and auditory information. Assessments for this memory domain usually involve repeatedly presenting participants with simultaneous visuospatial and auditory information, encouraging them to form a novel association between the two formats of data. In the assessment of memory encoding and recall, one format (visuospatial or auditory) is presented and the degree to which the participant correctly identifies the associated format is measured, to assess the success in encoding and retrieving this novel associative memory. For example, if a sound is associated with a visual stimulus on one side (e.g. left) of the presentation screen in the familiarisation trials, in the test trial the sound is presented alone, and the proportion of looking to the target location (e.g. left) is measured. If this proportion is significantly greater than chance, then it can be concluded that the association has been successfully encoded and retrieved.

Neural integration of visual and auditory information is coordinated by the posterior superior temporal sulcus (STS) and middle temporal gyrus (Beauchamp, Lee, Argall, & Martin, 2004; Calvert, 2001). These brain areas are activated by both formats of data, and process both simultaneously, facilitating associative memory encoding (Beauchamp et al., 2004). In brief, neurons in the STS map multiple formats of sensory inputs to the same neural location, permitting neuronal integration of information. These cells are called multisensory integrative cells,

which have been shown to fire at rates greater than that of the summed rates triggered by single format sensory stimulation (Beauchamp et al., 2004; Hughes, Reuter-Lorenz, Nozawa, & Fendrich, 1994; Stein, Meredith, & Wallace, 1993). Due to connections between the STS and the premotor superior colliculus, the appropriate orientation responses can then be made, these are faster for multi-format than single format stimulus inputs (Harris & Keynes, 1980; Hughes et al., 1994). The finding that both neuronal firing rates and reaction times are faster for associative than single format stimuli provides structural and functional evidence for specific associative memory encoding and response.

Studies pairing auditory tones with visual stimuli have shown that the presentation of the auditory stimulus alone causes activation in the visual cortex and vice versa (McIntosh, Cabeza, & Lobaugh, 1998). These results represent the neural connections in the STS responsible for the encoding and retrieval of visual-auditory associative memories (Barraclough, Xiao, Baker, Oram, & Perrett, 2005). There are some data suggesting that visual information is more salient than auditory information, implying that associative recall may occur more reliably if the test stimuli presented are visual rather than auditory (Pezdek & Stevens, 1984).

Some evidence suggests that impairments in associative LTM performance in participants over the age of 60 years are associated with increased risk for AD and other dementias (Crutcher et al., 2009). Either impaired encoding or retrieval of associative information could cause this. Therefore, changes in associative memory abilities, and thus underlying structural pathways, are implicated in later life neurodegenerative diseases. Although this thesis does not cover the consequences of neurodegenerative disease, the increased risk of AD in the DS

population makes the implication of this memory ability of interest when considering future outcomes (Mccarron, Mccallion, Reilly, & Mulryan, 2014).

6.1.2 Associative memory in typical development

Binding memory, a term used to describe associative memory, was discussed in 5.1.1 Visuospatial memory. Although binding memory is a terminology used in associative memory, Chapter 5 focused on within-format binding, whereas this study examines between-format binding. For TD individuals to form novel associative memories such as those assessed in experimental paradigms, it is necessary for individuals to be able to encode and manipulate novel multi-format combinations in STM and WM. This requires a different group of processing pathways to the accessing of LTM episodic memories, and it is these pathways that are discussed herein. Therefore, episodic memory, whilst being a form of associative memory and briefly discussed, is not the focus of this study.

Analysis of TD associative verbal memory assessed with word pair list-learning, showed verbal associative abilities improved steeply to age 8 and gently until 11 years old, at which point the developmental trajectory plateaued (Thaler et al., 2013). However, cognitive processing abilities of different modes of information develop at different rates. Binding and recall of two visually input forms of information, object and context information, improved between the ages of 4 and 6 years, at which point it appeared to reach adult levels (Sluzenski, Newcombe, & Kovacs, 2006). However, recognition abilities were equal in both age-groups, implying object-context associative recognition had reached adult levels by age 4 years (Sluzenski et al., 2006). Conversely, associations of object and location recall and word-pair recognition improved throughout childhood and early adolescence

(Cowan et al., 2006; Shing, Werkle-Bergner, Li, & Lindenberger, 2008). Visual 'what' associative memory develops until around 10 years of age, spatial 'where' associative memory develops until early adulthood, whereas temporal 'when' associative memory increases until around 9 or 10 years of age and then plateaus (Guillery-Girard et al., 2013). This difference in developmental trajectories of different associative abilities indicate potential differences in maturation of the neural structures responsible for the different processes. In addition to the disparity between the developments of different forms of memory, these different forms of memory develop in association with different cognitive abilities. For example, development of verbal fluency and temporal associative memory abilities are significantly correlated (Guillery-Girard et al., 2013). These examples illustrate the variability within associative memory recall and recognition trajectories, and highlight the importance of specificity when reporting design and results of current and past research.

Much of the previous literature on spatial-auditory associative memory is based on naturally occurring associations such as speech sounds and mouth movements, or animals and their calls (Beauchamp et al., 2004; Flecken, 2011; Shukla, White, & Aslin, 2011). These endogenously- meaning real world- associated stimuli are processed in a different manner to novel stimulus associations, and rely on LTM function. The effect of non-meaningful associations, such as music and object associations, are less well characterised. Previous research has shown that TD participants looked to spatial locations when attempting to recall details of stimuli that were presented in those locations (Richardson & Spivey, 2000). This result occurred when either visual or auditory information had been associated with a spatial location, showing how spatial recall can be assessed with multi-

format associations (Richardson & Spivey, 2000). The hippocampus was found to be essential to both recall and recognition of multi-format stimuli (Wixted & Squire, 2011).

When assessing the developmental trajectory of any cognitive feature, it is important to consider the real world validity of the assessment. Those assessments with lower ecological validity are less likely to produce generalisable findings than those closer to real-world situations. In this study we examine the novel binding of spatial and auditory data. The majority of studies of spatial-auditory binding focus on speech abilities. Although these findings are interesting, speech is a specialised human ability and does not reflect the ability of an individual to associate novel auditory-visual data.

Associative memory can be assessed numerous ways. One method that requires a low level of cognitive control is eye-tracking. Previous eye-tracking studies assessed adult associative memory by familiarising a face within a specific scene, and then displayed the scene with three faces, one previously associated, and the other two familiar but not associated with the scene (Hannula, Ryan, Tranel, & Cohen, 2007). These studies analysed looking to the familiar face in the window 500-700 milliseconds post-presentation, to measure recall of associated memories (Hannula et al., 2007). Infant studies of 9 month-olds using the same task have shown the first 1000 milliseconds to be the best measure of associative memory in eye-tracking tasks (Richmond & Nelson, 2009). This study also showed that in infancy if the test was presented without an interval, then the first 250 milliseconds contained the data where looking to the correct face was above chance, whereas if there was a small delay in test presentation then the 500-750 milliseconds time window was when the infants performed best. Previous studies of episodic memory

encoding in TD participants have presented the stimuli for around 7 seconds each, with trials separated by a central stimulus that required fixation for the visuospatial task to commence (Weber, Wang, Born, & Inostroza, 2014).

Although associative memory abilities develop throughout childhood, at low levels of control, individuals are capable of forming associations prior to the complete development of associative memory abilities and related cognitive domains (Munakata, 2001). Eye-tracking paradigms using the face-scene familiarisation and presenting the scene with the familiar face and two novel faces, showed infants as young as 9 months of age were capable of encoding and recognising familiar stimuli, although other studies have shown there was some variability in the onset of this ability (Munakata, 2001; Richmond & Power, 2014). TD infants aged 3, 6 and 10 months successfully performed in a paradigm associating a spatial location with an auditory stimulus, the same paradigm used in the current study (Kirkham, Richardson, Wu, & Johnson, 2012; Richardson & Kirkham, 2004). There were no significant effects of recency reported in these studies when infants were required to learn a sequence of associations prior to test trials.

6.1.3 Associative memory in Down syndrome

As associative memory function requires hippocampal function, and the hippocampus is a specifically atypical structure in the DS population, it was expected that associative memory would be impaired in DS (L. A. Miller, Muñoz, & Finmore, 1993; Pennington et al., 2003). Visual-verbal associative memory appears appropriate for the general level of cognitive ability in the DS population, although these tasks involved naming animals, numbers and letters and so measure LTM

abilities rather than associative WM (Marcell, Busby, Mansker, & Whelan, 1997; Ypsilanti, Grouios, Zikouli, & Hatzinikolaou, 2006). Associative memory abilities were correlated with the development of IQ in TD individuals, whereas the IQ trajectory in the DS population is reduced and the development of general cognitive ability is impaired, again suggesting that associative memory abilities would be delayed compared to TD individuals (Pennington et al., 2003). In a sample of individuals with DS aged between 13 and 23 years, associative memory was better than in a CA-comparable group with Williams syndrome (WS), most notably in the visuospatial Cambridge neuropsychological test automated battery (CANTAB) task (Edgin, Pennington, & Mervis, 2010). Abilities in this task significantly correlated with adaptive behaviour in the DS population, but not IQ, or verbal immediate or delayed recall (Edgin, Pennington, et al., 2010). Therefore, cross-sectionally assessed visual-spatial associative memory in the DS population appeared only to correlate with adaptive functioning, as assessed by the Scales of Independent Behaviour-Revised (SIB-R) overall standard score (Schrank, 2014), which includes motor, social, personal and community sub-domains (Edgin, Pennington, et al., 2010). Participants with DS age 3 to 5 years old compared to TD individuals matched on receptive language abilities, were not significantly impaired in an associative memory task requiring binding of a sequential presentation of objects, i.e. when the yellow square is presented, the blue triangle comes next, and the dependent variable is looking time to the familiarised sequence compared to a novel sequence. However, there was an effect of trial, where the TD participants looked significantly more on the first trial, but there was no difference on the second trial, due to decreased TD looking (Roberts & Richmond, 2015). This

implies that at young CA the most informative data can be collected from the first test trial, and there may not be any advantage in presenting multiple trials.

Visuospatial associative learning, assessed using object-location pairing from the CANTAB paradigm, appeared impaired in the DS population compared to TD individuals matched on KBIT-II raw scores between aged 7 and 38 years (Edgin, Mason, et al., 2010). In this sample, associative learning and memory were significantly correlated with prefrontal and cerebellar measures of reaction time, NEPSY track tracing, and set-shifting assessments. Others have shown that although spatial WM, assessed by the Corsi block task, was not impaired compared to SBIS-matched TD individuals, adding a visual component, which induces the need for associative memory function, impaired the DS populations abilities between aged 8 and 21 years (Visu-Petra et al., 2007). These results indicate that hippocampal function, as responsible for the encoding and retrieval of associative memory, is impaired in the DS group (Wang et al., 2014). Theoretically the episodic buffer is responsible for integrating associative memory data, implying the function of the episodic buffer may also be impaired in DS (Baddeley, 2000). Overall, compared to TD participants matched on intelligence tests, those with DS appeared impaired in associative memory tasks, at least within the visuospatial format. Although associative memory can correlate with IQ in the TD population, in the DS population it correlated with adaptive behaviour, prefrontal and cerebellar measures, more specifically, measure of inhibition and motor function.

6.1.4 The current study

The vast majority of previous assessments of associative memory have required a high degree of cognitive control, such as the CANTAB task. In this study

it was decided to assess associative memory at the lowest possible level of control using eye-tracking, requiring only eye gaze to produce a dependent variable. Eye-tracking measures can easily be obtained from infancy onwards, making it the ideal measure for an atypical population with a wide range of abilities (Johnson, 1994). As is seen in TD infants, eye-tracking signals from participants with DS of all ages are noisy; therefore instead of analysing fixations to the target, standard protocol is to use overall looking times to target (Johnson, 1994; Richardson & Kirkham, 2004). The formats of memory assessed herein were association of a location and a sound, previously validated in TD infants (Richardson & Kirkham, 2004). The former was a cartoon animal moving within a location, and will be referred to as spatial. The latter was a non-verbal stimulus and is referred to hereafter as auditory. This study was novel in examining associative memory abilities at low levels of control, and comparing the development of these abilities across development in CA-matched DS and TD groups. As the paradigm did not require any active response, WM could not be assessed by immediate STM was assessed, as was LTM after a delay of 15-20 minutes.

This study used eye-tracking to assess the formation of novel associative multi-format memories in early and late childhood in participants with DS. No active recall was required, so this may be interpreted as an implicit task. Vicari (2001), showed participants with DS were not impaired on multiple implicit tasks, including the Tower of London and word stem completion compared to TD individuals matched for the SBIS (Vicari, 2001). However, the target of this study was the formation of novel associative memories, which required hippocampal function. Although the low-demand nature of this task may compensate for some cognitive impairments in the DS population, the primary hypothesis was that the DS

group would be impaired on spatial-auditory paired associate learning in both STM and LTM, compared to the CA-matched TD group, based on the overall impairment previously observed (Edgin, Mason, et al., 2010; Visu-Petra et al., 2007).

Although previous work has not compared trajectories between DS and TD groups, based on the correlation of associative memory development and other cognitive measures including inhibition and motor function, the secondary hypothesis was that the two groups would improve at similar rates over development, assessed by a cross-sectional correlation with CA (Edgin, Mason, et al., 2010). Both immediate and delayed test trials of associative memory were presented to the participants. Based on the findings of Marcell (1997) that LTM associative memory abilities appeared MA appropriate (Marcell et al., 1997), the third hypothesis was that the change in performance between immediate and delayed associative memory trials would not be significantly different across development between DS and TD groups, indicating that encoding of associative memory information was not impaired.

Due to the previously noted correlation between associative memory and adaptive behaviour (Edgin, Mason, et al., 2010), a measure of adaptive behaviour was collected in this study, the Vineland Adaptive Behaviour Scale (S. Sparrow, Cicchetti, & Balla, 2005). Measures from the Vineland were correlated with associative memory measures, as well as CA, non-verbal raw score measured by pattern construction and verbal score derived from the BPVS. No previous work has assessed spatial-auditory associative STM or LTM in the DS population, nor their relationship with development, making this study innovative.

6.2 Methods

6.2.1 Participants

Participants with and without DS were recruited as described in 2.2 Participants. Forty-three participants with DS were recruited between the ages of 4 and 15 years old. Thirty-two TD participants were recruited between the ages of 4 and 15 years old. Eight participants with DS and 5 TD participants were excluded due to failure to attempt the task. This was not due to cognitive limitations, but technical difficulties or behavioural issues. Therefore, the low control nature of this task permitted everyone who was able to sit in front of a screen to take part in the task was included and there were no cognitive reasons for exclusion. One further TD participant in both early and late childhood was excluded for yielding insufficient data for analysis. Therefore, the groups consisted of 35 participants with DS and 25 TD participants in age-groups outlined in Table 6.1. Four of the excluded participants with DS were in the early childhood group, the other four were in the late childhood group. Three of the excluded TD participants were in the early childhood group, and three were in the late childhood group. Two of the participants with DS in the early childhood group only completed the immediate test trials, and not those after a delay, and were only included in the analysis of the former. Table 6.1 summarises the group profiles for immediate and delayed test trials.

Table 6.1 The mean CA and SD of participants included in the associative memory study, in both immediate and delayed conditions

	Early Childhood		Late Childhood	
	DS	TD	DS	TD
Immediate test trials				
Mean CA months	74.00	70.75	148.18	138.69
(SD)	(19.58)	(18.28)	(22.12)	(18.89)
N	18	12	17	13
Immediate and Delayed test trials				
Mean CA months	72.63	70.75	148.18	138.69
(SD)	(19.85)	(18.28)	(22.12)	(18.89)
N	16	12	17	13

6.2.2 Procedure

In order to minimise the cognitive demand of the task, and to mimic previous work done with mouse models of DS, an eye-tracking paradigm was decided to be most appropriate to measure spatial-auditory associative memory (Hall et al., 2016). The paradigm used was based on one previously validated in TD infants, making it appropriate for those of low MA (Richardson & Kirkham, 2004).

6.2.2.1 Paired associate learning

Paired associate learning is a measure of integrative and associative memory. This task was based on the Richardson & Kirkham (2004), study, designed to assess spatial indexing. During eight familiarisation trials, participants learned to associate the location of one image (moving slightly within a frame) that was consistently presented on one side of the screen with a simultaneously presented specific sound, and another image on the other side of the screen with a simultaneously presented different sound. Auditory stimuli were delivered via two speakers positioned behind the display monitor and facing the participant. In between each trial, an attention grabber was displayed in the centre of the screen, with the next trial only starting after the participant had fixated this point. Each familiarisation trial lasted 8 seconds, and each image and associated sound was displayed four times, as illustrated in Figure 6.1.

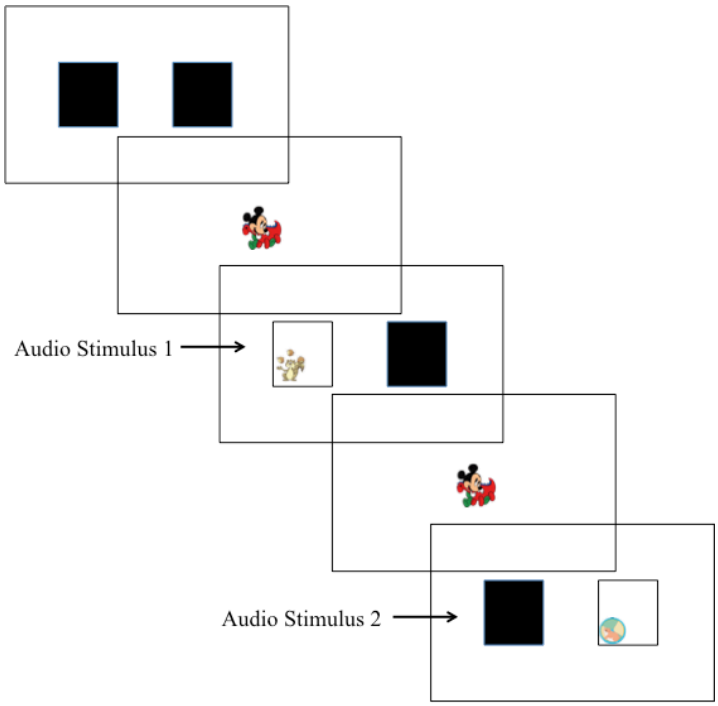

Figure 6.1 A schematic demonstrating the familiarisation trials of the associative memory paradigm

The attention grabber was also presented after familiarisation and before the test phase. In the first test trial, participants heard only one of the previously presented sounds for 8 seconds but did not see any image in either of the two frames. Another attention grabber guaranteed that the participants fixated the centre of the screen, after which the other sound was presented during the second test trial, as illustrated in Figure 6.2. The whole procedure lasted 2 minutes. There was also a delayed aspect to this test, where after an interval of at least 15 minutes and not more than 30 minutes, the test trials alone were displayed again, without any familiarisation of the study trials. The outcome of this test is the percentage looking time to the target side of the screen, as a measure of associative learning.

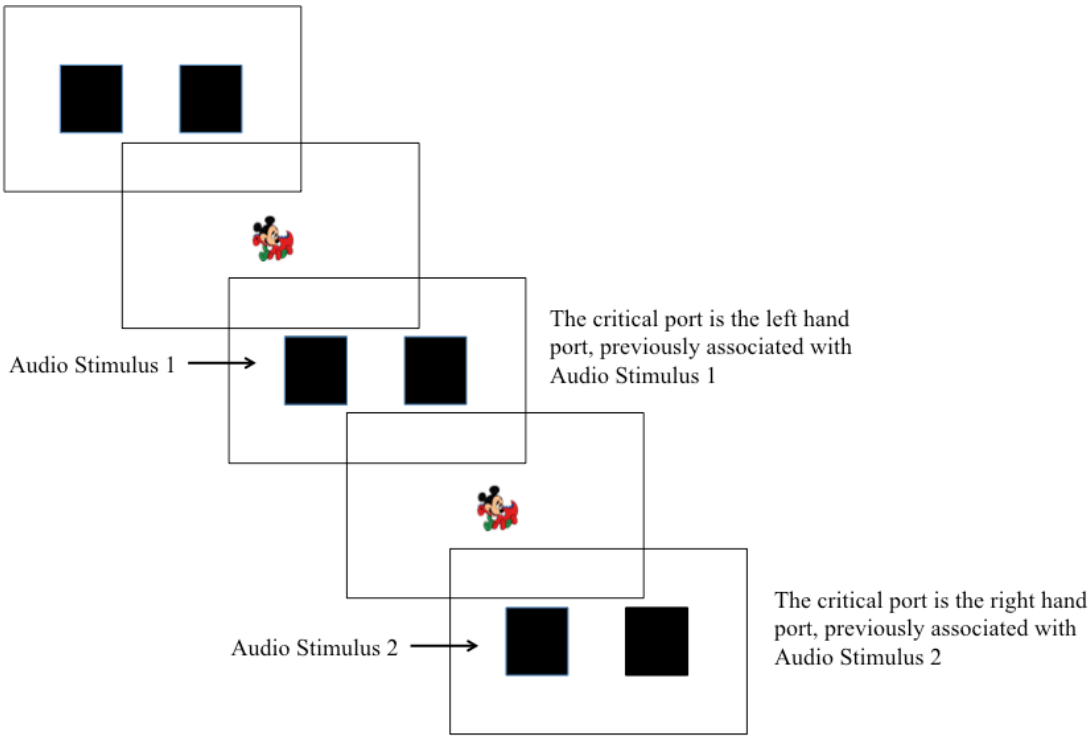

Figure 6.2 A schematic demonstrating the test trials of the associative memory paradigm

In addition, a subtest of the British Ability Scale 2 was administered, pattern construction, to calculate non-verbal abilities. The BPVS was administered to

calculate verbal abilities. The administration of these assessments was outlined in Chapter 2.

Inclusion in this task was defined by the paradigm itself. Familiarisation trials were not presented unless eye-gaze was detected, therefore the task would not proceed without behavioural compliance. Therefore, all participants who attempted this task were included in analysis, irrespective of how many valid samples were obtained.

Some features of the paradigm were altered for this assessment, for example, the number of exposures to familiarisation and test trials were consistent, whereas in the original study infant behaviour determined the number of repetitions. The same two visual stimuli were used for all participants, whereas in the original study there were six visual stimuli and their presentation was randomised. In addition to this, in the original study the order of test trial presentation was randomised, whereas in this study the first test trial was never the same as the last familiarisation trial. The exposures to trials were made consistent to limit the time taken for this task and prevent boredom if the stimuli were presented continuously; the same two stimuli were used for consistency. The familiarisation trials were increased from 6 to 8 to increase the likelihood of looking to the familiarisation stimuli. Overall, this task was appropriate for those of the youngest MA in the study, was inclusive of participants with physical disability, as it only requires eye gaze and low-level cognitive control, and could be administered in a short period of time.

6.2.3 Design

The study had both within and between group factors. Between groups were the participant groups of DS and TD and the age-groups of early and late childhood. Thus, the independent variables were group and age-group. The dependent variable was proportional total looking time (PLT) to the critical port in both immediate and delayed trials, and change between these two exposures to the test trials. PLT was used rather than absolute looking time as the participants with DS had reduced overall looking time to the stimulus display. This was either a true measure of behaviour, or caused by the eye-tracker being insufficiently sensitive to capture irregular gaze patterns. It could not be concluded which of these suggestions is more accurate, although when carrying out the tasks, it was observed that the eye-tracker failed to consistently measure the gaze of many participants with strabismus or who did not look at the stimulus screen straight-on. Also because of the issues with eye-tracking in the DS population, the looking time in both STM and LTM were averaged across the two test trials to provide a more reliable measure.

6.2.4 Analysis

Statistical analyses were carried out with IBM SPSS Statistics, Version 20 (IBM, 2011). Extraction of the desired samples from the overall data was carried out using MATLAB scripts (MathWorks, 2012). The outcome measure of the eye-tracking paradigm is the coordinates of the eyes on the screen, at a rate of approximately 120 samples per second. Therefore, the outcome was a “number of samples”, rather than a measure of time. However, due to the direct linear relationship between sampling and time, it can be inferred that more valid samples

in a trial correspond to longer a looking time. The test trial looking times were analysed as proportions of overall looking time to the critical port in each test trial, as demonstrated below. Due to the implicit nature of this task, it was necessary to assess if the behaviour was merely at chance levels, therefore the proportional looking time was compared to chance (50%) in both groups, and where appropriate, age-groups within groups.

PLT= (LOOKING TIME TO CRITICAL PORT/ TOTAL LOOKING TIME)*100

6.3 Results

6.3.1 Characterisation of the population

The mean verbal and non-verbal measures of the groups was calculated from pattern construction and BPVS for those who completed either only trial 1 or both trials are outlined in Table 6.2.

Table 6.2 The mean and SD raw score calculated from pattern construction component of the British Ability Scale and MA from the BPVS, with N that successfully completed immediate and immediate and delayed test trials

	Early Childhood		Late Childhood	
	DS	TD	DS	TD
Immediate test trials				
Mean Pattern Construction raw	8.60	27.75	12.75	40.08
(SD)	(5.85)	(14.90)	(7.46)	(13.44)
N	10	12	16	13
Mean Verbal score	40.06	86.33	68.38	140.92
(SD)	(17.50)	(23.75)	(18.15)	(14.81)
N	18	12	17	13
Immediate and Delayed test trials				
Mean Pattern Construction raw	8.60	27.75	12.67	40.08
(SD)	(5.85)	(14.90)	(7.72)	(13.44)
N	10	12	15	13
Mean Verbal score	41.80	86.33	68.38	140.92
(SD)	(17.85)	(23.75)	(18.15)	(14.81)
N	16	12	17	13

6.3.2 Familiarisation trials

A T-Test was used to compare the looking to each side of the screen in the familiarisation trials. There was not a significant preference for either side of the screen in either group: TD ($t(25)=1.11$, $p=0.280$, $\eta^2=0.015$); DS ($t(34)=0.717$, $p=0.478$, $\eta^2=0.047$). A repeated measures ANOVA was conducted to examine the effect of group on familiarisation looking time to the screen, the DS group (M=154.00, SD=48.3) looked significantly less to the screen than the TD group (M=207.56, SD=65.7) over familiarisation trials ($F(1,58)=17.17$, $p<0.001$, $\eta_p^2=0.225$), therefore in all further analyses PLT was used.

6.3.3 Overall associative memory performance

A repeated measures ANOVA was conducted to examine the effect of age and group on PLT in immediate and delayed associative recall. There was no significant main effect of age, $F(1,54)=0.42$, $p=0.518$, $\eta_p^2=0.008$. The main effect of group was significant, the DS group looked significantly less to critical port, $F(1,54)=14.49$, $p<0.001$, $\eta_p^2=0.212$. However, the group by age-group interaction was non-significant, indicating the change between immediate and delayed associative recall was not significantly different between the groups across development, $F(1,54)=1.21$, $p=0.276$, $\eta_p^2=0.022$. Looking at the data as in Figure 6.3, it appears that although the change from immediate to delayed trials was not significantly different between the early and late childhood TD groups, and the DS early childhood group, the late childhood DS group appears to behave differently, suggesting further investigation may be warranted.

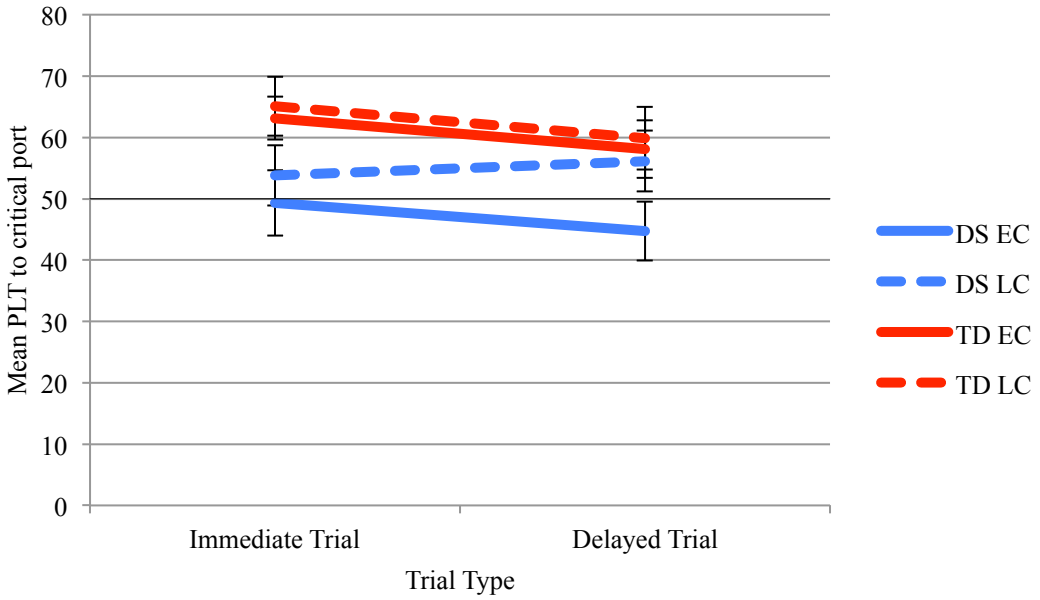

Figure 6.3 PLT to the critical port in immediate and delayed test trials in early and late childhood in DS and TD groups. Chance is marked with a horizontal line at 50%. Error bars represent +/- 1 SE

6.3.4 Immediate associative memory test trials

Averaging the PLT over the immediate trials, a two-way ANOVA was conducted to examine the effect of age and group on immediate associative recall. There was a significant main effect of group, with the DS group looking significantly less to the critical port ($F(1,57)=11.49$, $p=0.001$, $\eta_p^2=0.168$). The main effect of age-group ($F(1,57)=0.71$, $p=0.402$, $\eta_p^2=0.012$) and the group by age-group interactions were non-significant ($F(1,57)=0.13$, $p=0.720$, $\eta_p^2=0.002$). These findings mean that pooling the data there was not a significant improvement in immediate associative memory abilities over development, and that the relationship between associative memory abilities between early and late childhood were not significantly different between groups.

Comparing the PLT to chance, the DS group looking to the critical ports was not significantly different from chance ($t(34)=0.64$, $p=0.526$ $\eta^2=0.012$), therefore this paradigm did not detect the operation of spatial-auditory associative STM in the DS group. The TD group performed significantly above chance ($t(24)=4.93$, $p<0.001$, $\eta^2=0.493$). The fact that the TD group performed above chance supports the previous finding that this paradigm is appropriate for measuring associative memory in the TD population.

Given the non-significant interaction effect of group and age-group, it appears the two groups improved over childhood at similar rates, as shown in Figure 6.4, where neither group appears to improve significantly over childhood.

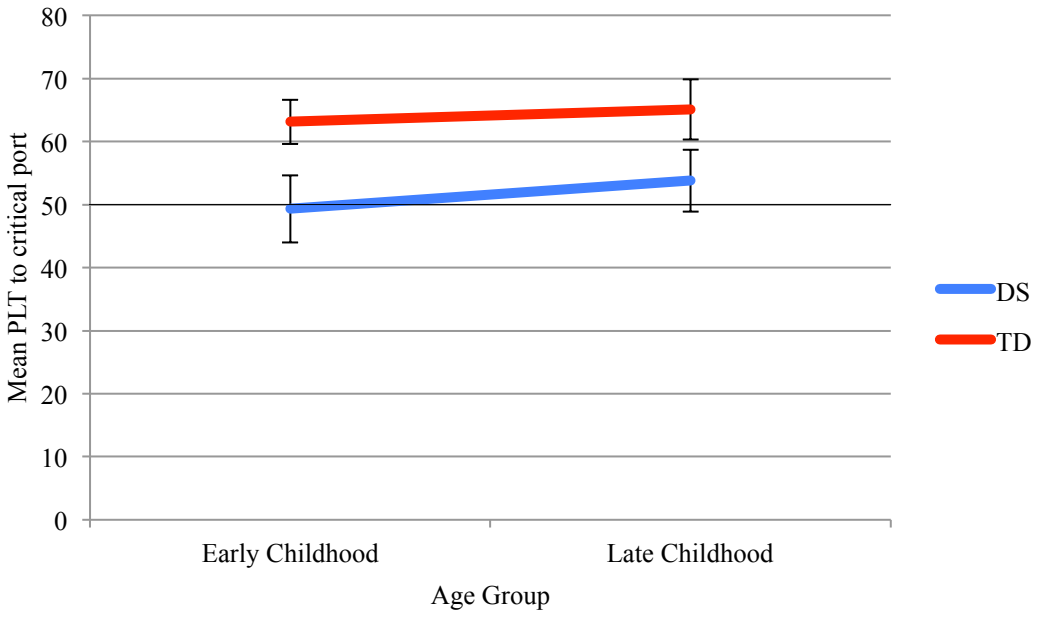

Figure 6.4 PLT to the critical port in immediate test trials over early and late childhood in DS and TD groups. Chance is marked with a horizontal line at 50%. Error bars represent +/- 1 SE

6.3.5 Delayed associative memory test trials

Averaging the PLT over the delayed trials, a two-way ANOVA was conducted to examine the effect of age and group on immediate associative recall. There was a significant main effect of group, with the DS group looking significantly less than the TD group to the critical port ($F(1,54)=4.84$, $p=0.032$, $\eta_p^2=0.082$). The main effect of age-group ($F(1,54)=2.87$, $p=0.096$, $\eta_p^2=0.051$) and the group by age-group interaction effects were non-significant ($F(1,54)=1.55$, $p=0.219$, $\eta_p^2=0.028$). Therefore, the relationship of associative LTM development was not significantly different between groups, and neither group significantly improved over age.

Comparing these PLT to chance, the DS group were not significantly different from chance ($t(32)=0.23$, $p=0.411$, $\eta^2=0.001$). The TD group performed significantly above chance ($t(24)=3.07$, $p=0.003$, $\eta^2=0.282$), see Figure 6.5. Due to the unusual slope of the DS line across childhood, the data were divided into age-groups and the difference from chance was analysed. While in early childhood the DS group were not significantly different from chance ($t(15)=-1.397$, $p=0.092$, $\eta^2=0.115$), in late childhood the DS group were ($t(16)=1.852$, $p=0.042$, $\eta^2=0.176$).

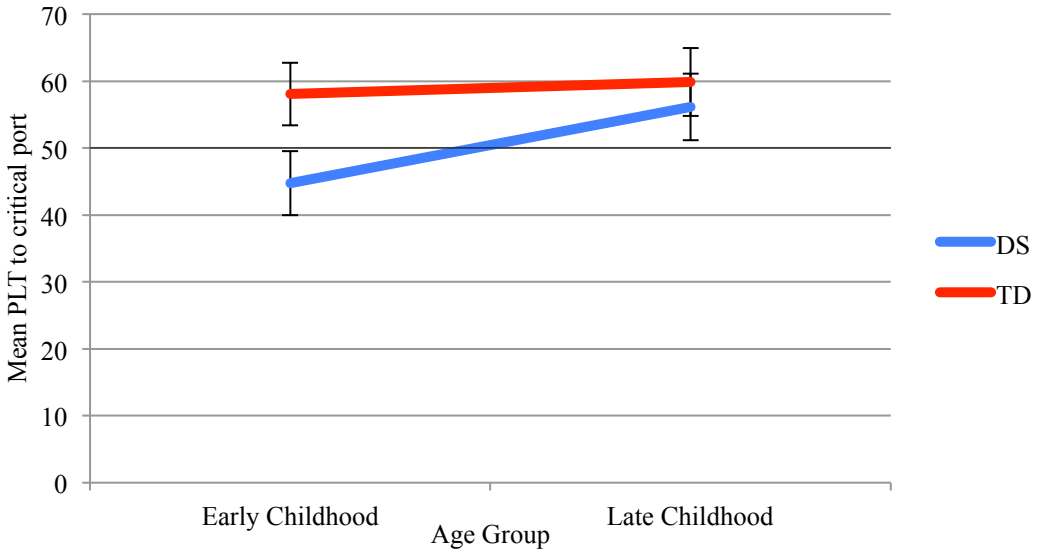

Figure 6.5 PLT to the critical port in delayed test trials over early and late childhood in DS and TD groups. Chance is marked with a horizontal line at 50%. Error bars represent +/- 1 SE

6.3.6 Correlations between immediate and delayed associative memory and CA, adaptive, verbal, and non-verbal measures

To assess if the immediate and delayed associative memory abilities were associated with CA, non-verbal raw score, verbal score, or adaptive behavioural measures, correlation analyses were carried out, as shown in Table 6.3. The standardised score of the Vineland was included, as was non-verbal raw score calculated from pattern construction, a subtest of the BAS 2. Verbal score, derived from the BPVS, was also correlated with associative STM and LTM. Higher standardised scores are indicative of better adaptive behavioural abilities, and higher verbal and non-verbal scores are indicative of better abilities. Therefore, if these abilities are associated with associative STM and LTM the correlations should be positive.

The only significant correlations were in the DS group between associative LTM performance and CA and verbal score. The lack of other significant correlations prohibits any further interpretation of the relationship between variables or groups. Due to the significant correlation of CA and LTM in the DS group, this was further investigated. The data were divided into group and age-group and the difference from chance was analysed. While in early childhood the DS group were not significantly different from chance ($t(15)=-1.397$, $p=0.092$, $\eta^2=0.115$), in late childhood the DS group were ($t(16)=1.852$, $p=0.042$, $\eta^2=0.177$). The TD group was significantly above chance in both age-groups (early childhood $t(11)=2.171$, $p=0.027$, $\eta^2=0.300$; late childhood $t(12)=2.135$, $p=0.027$, $\eta^2=0.275$). The difference in means were analysed, and although in early childhood the groups were significantly different ($t(26)=-2.46$, $p=0.021$, $\eta^2=0.189$), in late childhood the DS and TD associative LTM abilities were not significantly different, $t(28)=-0.67$, $p=0.507$, $\eta^2=0.015$.

Table 6.3 Correlation coefficients, significance and N for immediate and delayed associative memory trial PLT to targets and CA, ABC (adaptive behaviour composite standard score), non-verbal raw score (derived from pattern construction) and verbal score (derived from the BPVS), split between DS and TD groups.

Group	Measure	Statistic	CA (months)	ABC	Non-verbal raw	Verbal score
DS	Immediate Trial	Pearson Correlation	0.085	-0.121	0.145	-0.159
		Sig. (2-tailed)	0.627	0.517	0.481	0.378
		N	35	31	36	33
	Delayed Trial	Pearson Correlation	0.387*	0.100	0.264	0.403*
		Sig. (2-tailed)	0.026	0.607	0.201	0.025
		N	33	29	25	31
TD	Immediate Trial	Pearson Correlation	0.154	0.305	0.139	0.210
		Sig. (2-tailed)	0.461	0.178	0.506	0.314

	N	25	21	25	25
Delayed Trial	Pearson Correlation	0.199	-0.378	0.141	0.007
	Sig. (2-tailed)	0.340	0.091	0.502	0.973
	N	25	21	25	25

*p<0.05, **p<0.005

6.4 Discussion

Overall, there is some discussion needed over whether the paradigm successfully measured associative memory in the DS group, as performance was not significantly better than chance in either age-group in the immediate test trial, or in early childhood in the delayed test trial. However, the fact that this paradigm has been validated in TD infants, and that all TD groups performed above chance in this study, indicates that this is an appropriate paradigm to assess associative memory in typical development and at low MA levels. Typical associative memory abilities were absent in the DS group, except for delayed associative memory abilities in the late childhood group. However, the fact that there was a group who performed above chance in this assessment suggests it is an appropriate measure of associative memory in DS, but that DS associative memory functions in a different way than in TD, as will be discussed in detail later. It is always possible that participants with DS have associative memory abilities that could be captured by another paradigm, but speculation on that point is somewhat arbitrary here, where the focus is on the outcome of this specific spatial-auditory associative memory assessment.

The initial hypothesis that associative memory in the DS group would be impaired overall compared to the TD group was supported by the omnibus analysis of immediate and delayed associative memory, where the DS group looked significantly less to the critical port than the TD group overall. However, the effect size was small so this relative impairment must be interpreted with caution.

It was hypothesised that the two groups would improve at similar rates over development. To support this, in both immediate and delayed trials, and the overall

analysis, the interactions of group and age-group were non-significant. However, at no point was the main effect of age-group significant, indicating that when combining the groups there was not a significant improvement in associative memory overall, when immediately assessed, or after a delay, across CA. Therefore, there was no evidence that the two groups' associative memory skills developed at significantly different rates over early and late childhood, it is possible this similarity in development over CA is driven by the fact that neither group improved significantly with age. The suggestion that the TD group did not significantly improve with CA is supported by previous literature suggesting some forms of associative memory have reached adult levels at younger CA than those included in this study (Sluzenski et al., 2006). This result suggests that spatial-auditory associative memory also has reached adult-like levels by this age in TD individuals. Contrastingly, in the DS cohort, it is possible that neural structures associated with LTM spatial auditory associative STM, perhaps including the posterior STS and middle temporal gyrus, continue to mature across childhood.

Some reports have linked impaired LTM associative function to increased risk of AD (Crutcher et al., 2009). However, in this DS sample LTM associative memory performance improved with developmental time, as indicated by a conversion from non-significantly different from chance in early childhood to significantly above chance performance in late childhood. The result that low-control associative LTM was not atypical in late childhood warrants further characterisation of this ability. If in later life it still appears relatively typical it may prove to be a sensitive measure of function impairment onset in atypical populations.

The third hypothesis was that the change in performance between immediate and delayed associative memory trials would not be significantly different across development between DS and TD groups, indicating that encoding of associative memory information was not impaired. This was statistically supported by the omnibus analysis, which found no significant three-way interaction between group, age-group, and trial. This is a novel finding of CA-appropriate development of long-term encoding and retrieval of associative memories in the DS population.

Due to previous reports of associations between adaptive behaviour and associative memory performance (Edgin, Mason, et al., 2010), measures of adaptive behaviour were correlated with both immediate and delayed associative memory performance. In the DS group, no significant correlations were found between adaptive scores and associative memory abilities, although CA and verbal abilities correlated with performance in the delayed test trials. This indicates that in the DS group, spatial-auditory associative LTM improved with CA, and this improvement was comparable to verbal ability development. No such correlations were found in the TD group, implying that TD spatial-auditory associative memory did not improve over childhood, or in-line with other cognitive measures. The most likely explanation of the latter null finding is that individuals have reached near maximal levels in early childhood, preventing significant improvement over late childhood. This is not to say that in other tasks TD children do not improve in associative memory abilities over childhood, but in this low-cognitive demand task, it is possible that the required abilities are already fully developed in early childhood. No significant correlations with adaptive or pattern construction skills were found in the TD group.

Overall, the improvement in associative LTM abilities across childhood in DS, which is not seen in TD participants, suggests that the hippocampus, and the posterior STS, may develop for longer in the DS population than in TD individuals. Alternatively, other, later developing brain regions, may also contribute to these abilities, which are not involved in TD associative memory abilities. Further, functional imaging, studies, are required to accurately identify brain regions associated with cognition in atypical populations such as those with DS. In addition to this, in TD individuals the auditory encoding is associated with the left MTL, whereas visuospatial are more associated with the right lobe. The left hippocampus is more microcephalic than the right in people with DS; implying verbal abilities may be more severely affected in people DS due to the volumetric losses in the left hemispheric limbic system (Jernigan et al., 1993). In atypical development, it is essential to ascertain the degree to which structural and functional alterations are related. For example, although it is tempting to draw parallels between the more microcephalic left hemisphere and relatively delayed verbal memory abilities, it is naïve to presume that the same structures responsible for these abilities in TD individuals are necessarily playing an identical role in a system that has developed atypically.

Previous literature had reported effects of recency on associative memory in TD infants (Kirkham et al., 2012). The current paradigm, which was slightly adapted from the original, was not designed to analyse this feature. The eight-familiarisation trials were randomised as left-right pairs, and over the four presentations of these pairs there was randomisation in whether the left or right was presented first. However, the task was designed so that the first test trial was always the opposite side from the most recent familiarisation trial. If the most

recent familiarisation was the left-hand side port, then the first test trial would be the right-hand side port associated sound track, and vice versa. This eliminated any possibility of assessing the effect of recency on associative memory, which was a limitation of this study. Future studies of associative memory could assess the recency effect in the DS population by randomising test trial presentation.

There was another limitation caused by the design of test trial presentation. Following fixation on the central stimuli, the ports were presented simultaneously with one of the audio stimuli. This prevented an assessment of any natural side preference. During the familiarisation trials, there was always an interesting visual stimulus to look at, and in the test trials there was no period without an auditory stimulus. Therefore, there was no period where natural preference for one side of the screen or another could be assessed. If any side preference could have been assessed, a better measure of memory could have been calculated, where this measure would have been subtracted from looking times to either side of the screen. Some data have suggested that associative memory is better tested if the stimulus is visual rather than auditory (Pezdek & Stevens, 1984). A future study assessing associative memory in this multi-format manner could increase the performance of the DS group, and thus be more informative about the development of associative memory abilities.

Overall, spatial-auditory associative memory was impaired in those with DS compared to TD individuals across early and late childhood. The rate of improvement did not appear significantly different between the two groups over childhood. Spatial-auditory associative STM was not successfully assessed in this paradigm, or was not functioning at sufficient levels in the early childhood group. However, by late childhood people with DS were looking to the critical port

significantly above chance, implying that at this age participants with DS were able to successfully encode and retrieve spatial-auditory associative LTM. Therefore, hippocampal associative encoding was functioning in late childhood in participants with DS, similarly to CA-matched TD participants. Therefore, although spatial-auditory associative memory appeared to develop at a slower rate in those with DS than TD participants as assessed by the current paradigm, long-term encoding and retrieval of spatial-auditory associative recognition appeared behaviourally typical by late childhood. This is a novel finding, and suggests a potentially interesting relationship between the behaviour of STM and LTM in low-control associative format. Despite the DS group not performing above chance in the STM trials, the information was successfully encoded, as evidenced by typical LTM behaviour. Therefore, it is possible that the use of a single immediate assessment was not sensitive enough to detect this STM performance in late childhood, or that despite the absence of STM abilities, the information entered WM and thus LTM storage facilities successfully. The mechanisms behind this atypical encoding of between-format associative memory would be an interesting target of future research.

Chapter 7 Attention, Executive Function and Sleep

7.1 Introduction

In this section theories of attention and executive function are discussed. Features of attention, executive function, and sleep and their influences on TD memory abilities are then discussed, followed by a review of the literature addressing these abilities and their influence on memory function in the DS population. The current study is then described.

7.1.1 Theories of attention and executive function

7.1.1.1 Attention

Attention is the process of taking notice of something, by optimising sensory processing of that information. Attending to something is usually required for that event to be encoded into memory (Cowan et al., 1999; Schacter, Gilbert, & Wegner, 2011). Therefore, the ability to attend and focus has implications for academic outcomes, including language-learning and social development. One theory of attention is that it comprises three networks: alerting, orienting and executive; the latter is the central network, which is responsible for target detection and sustaining focussed attention to said target (Posner & Petersen, 1990). This then limits the networks' ability to detect another target, as the capacity of networks are finite (Petersen & Posner, 2012). Another theory of attention decomposes childhood and adolescent attentional domains into three: selective attention, sustained attention, and attentional control (Rueda et al., 2004, 2005). These two theories overlap, with selective attention equivalent to the orienting network, and attentional control equivalent to the executive network (M. Posner, 1987; Posner, Petersen, Fox, & Raichle, 1988). There are other theories of attention, sharing broad

common principles, for which we will not go into detail here (see (M. I. Posner, 2012) for recent review). Instead, the focus is on the development of attentional skills, using the terminology of the selective, sustained and attentional control model. Infant-based findings suggest a two, rather than three, factor attentional model, comprised of executive attention and sustained-selective attention (Steele, Karmiloff‐Smith, Cornish, & Scerif, 2012). In typical development, factor analysis of individual's scores on a battery of attention tasks indicated that the conversion from the two to three-component models of attention occurs between 4 and 5 years of age (Breckenridge, Braddick, & Atkinson, 2013). Therefore, when studying attention in the DS population, individuals either side of this MA could be examined to ascertain if the same two- to three-component shift occurs in the DS population as in the TD population.

In terms of the three-component model of attention, the focus of this study is sustained attention. This can be more precisely defined as when attention is given to a stimulus beyond the initial, reactionary, response. Sustained attention can be split into three distinct stages: attention getting, attention holding and attention releasing (Graziano, Calkins, & Keane, 2011). Selective and sustained attention involve inhibition of distraction to extraneous stimuli, allowing the individual to focus on the necessary information (Stevens, Lauinger, & Neville, 2009). Attentional control is the system responsible for both the inhibition involved in selective attention and the maintenance required for sustained attention (Lavie, Hirst, De Fockert, & Viding, 2004). Therefore, when testing sustained attention, attentional control abilities are also implicated. Furthermore, there is an overlap between the inhibition involved in attention and the inhibition referred to in executive function

literature, leading to potential confusion when using the term 'inhibition' (Diamond, 2014; Graziano et al., 2011).

7.1.1.2 Executive function

Executive functions are best described as an individual's cognitive flexibility. They allow and support planning, reasoning, execution, WM, inhibition, task switching, and impulse and emotional control (Diamond, 2014). Executive functions rely on many brain regions, notably the pre-frontal cortex (PFC), parietal regions, and the corpus callosum (Just, Cherkassky, Keller, Kana, & Minshew, 2007). Executive function is sometimes described as having hot and cold domains; hot executive functions involve emotional or motivational responses, and rely on the ventral-medial PFC (Hongwanishkul, Happaney, Lee, & Zelazo, 2005). Cold executive functions involve more detached, decontextualized problem solving and employ the dorsolateral PFC (Diamond, 2014; Hongwanishkul et al., 2005). Executive functions develop markedly over the first 5 years of life in TD individuals and then continue developing at a slower rate into adolescence (Anderson, 2002; Huizinga, Dolan, & van der Molen, 2006). Some authors propose that attention abilities are integral to the development of executive function capacity (Posner & Rothbart, 1998, 2007), whereas others argue it is the improvement of inhibition abilities that are essential to the development of executive functions (Dempster & Vegas, 1992). Whichever theory may prove to be correct, in the TD population many measures of executive function improve in a correlated manner, supporting the theoretical interpretation of executive functions as a unitary construct (Welsh, Pennington, & Groisser, 1991). However, evidence from lesion patients suggest that different executive function processes rely on different neural networks, and thus may be developmentally distinct (Dempster & Vegas, 1992; Miyake et al., 2000;

Welsh et al., 1991). Therefore, the theories of executive function have been integrated to allow for both attention- and inhibition-dependent executive function developmental processes, and the existence of independent and dissociable executive function components (Miyake et al., 2000). Miyake et al., (2000) defines the three executive functions as shifting, updating and inhibition. Updating is the same as WM, defined as 'information updating and monitoring'. Work by Diamond and colleagues defined the core executive functions as cognitive flexibility, WM and inhibition (Diamond, 2014). This theoretical overlap indicates concordance in the field that executive function is composed of inhibition, a function of WM, and a component of shifting or cognitive flexibility.

7.1.1.3 Summary of theories

Within these theories there is an overlap between attention and executive function in the role of inhibition. In some cases there are also 'executive functions of attention' referenced in the literature (Rueda et al., 2005). In essence, executive functions require attention, and attention can require inhibition and WM, so any measure of either ability will involve contributions from the other skill set. This overlap in features potentially contributing to a behaviour or research outcome will become relevant in the analysis of experimental findings.

7.1.2 Attention, executive function and sleep in typical development

7.1.2.1 Attention

Between aged 4 and 5 years, the conversion from a two to three component model of attention occurs (Breckenridge, Braddick, & Atkinson, 2013). Before the conversion, factor loading models divide attentional task abilities into 'sustained attention' and 'selection and response', whereas after the conversion, the factor

loading analysis resulted in three components: sustained attention, selective attention, and attentional control (Breckenridge, Braddick, & Atkinson, 2013). The focus of the current study, sustained attention, is measured in infancy and early childhood using length of looking time to a toy or an item onscreen (J. H. Brown et al., 2003; Gaertner, Spinrad, & Eisenberg, 2008; Graziano et al., 2011). Previous studies using these assessments have ranged from 45 seconds to 5 minutes in length, using the measure of overall looking time. Some authors refer to the first 5 seconds of attention as reactive attention, although this period can still be included in the analysis of sustained attention (Richards, 1987). Measures of visual and auditory sustained attention both significantly improved from aged 3 to 6 years in typical development (Breckenridge, Braddick, & Atkinson, 2013). In early development sustained attention is strongly correlated with verbal STM and LTM, assessed by memory for names and sentences (Coll, 2005; Cowan et al., 1999). Due to the overlap in definitions of attention, executive function and WM, the association of these abilities is not unexpected. Therefore, improved sustained attention should correlate with improved verbal STM and LTM over early childhood in the TD population.

7.1.2.2 Executive function

Factor loading model analyses of executive function in childhood have found in three factors or clusters between 8 and 13 years of age, and in adulthood; WM/updating of information, set shifting, and inhibition (Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003; Miyake et al., 2000). Other studies on individuals aged 3 to 12 years, have clustered executive function into speeded responding, set maintenance, and planning (Welsh et al., 1991). The studies used majority different tasks, which contributed to the different outcomes in terminologies used. These proposed

components develop rapidly but not synchronously across 3, 6, and 10 years of age (Diamond, 2001; Diamond & Taylor, 1996; Welsh et al., 1991). The Welsh et al. (1991) study also showed that speeded responding, set maintenance, and planning reached adult performance levels at 6 years old, 10 years old, and adolescence, respectively. This lack of synchronicity suggests that the abilities are reliant on non-identical neural pathways, supporting previously outlined theories (Miyake et al., 2000). Further investigation of executive function development suggests that frontal lobe function develops dramatically between the ages of 6 and 8 years, with slight increase in abilities up to 10 years of age, and adult level skills in place by 13 years of age (Lehto et al., 2003; Passler, Isaac, & Hynd, 1985; Rueda et al., 2004; Welsh et al., 1991).

Correlation analyses on executive function components across CA of 8 to 13 years of age found that although WM and updating did significantly improve with CA, inhibition did not (Lehto et al., 2003). Further studies assessing conflict monitoring showed executive control abilities did not improve past 7 years of age (Rueda et al., 2004). An earlier study of executive control using a set switching paradigm found that, although abilities improved between 3 and 6 years of age, at this point abilities appeared to plateau (Diamond & Taylor, 1996). Another study showed inhibition abilities developed rapidly between 3 and 4 years of age, and thereafter continues to slowly improve into late childhood (Jones, Rothbart, & Posner, 2003; Welsh et al., 1991). Inhibition abilities are specifically implicated in academic outcomes such as mathematics, English, science ability, and development of theory of mind (Bull & Scerif, 2001; St Clair-Thompson & Gathercole, 2006; Thierry, 2004). There is an overlap between the academic achievements influenced by inhibition and visuospatial WM abilities, implying these features may contribute

in a complementary manner to academic outcomes (St Clair-Thompson & Gathercole, 2006). The overall implications of these studies are that inhibition has undergone the majority of development before the ages included herein and no longer correlates with CA in late childhood. The development of inhibition is also implicated in the development of visuospatial WM abilities and academic outcomes.

7.1.2.3 Sleep

Longer and less disturbed sleep cycles in TD infancy are associated with better cognitive outcomes in later development (Borghese, Minard, & Thoman, 1995; Dearing, McCartney, Marshall, & Warner, 2001; Scher, 2005). Reduced sleep durations between aged 2 and 6 years of age are accompanied by worse verbal and non-verbal outcomes (Touchette et al., 2007). WM abilities are also associated with sleep duration between 6 and 13 years of age (Steenari et al., 2003). Declarative memory abilities in childhood, for instance assessed by word-pair recall, are improved by a period of sleep, whereas procedural memory abilities, such as finger sequence tapping, are not (Backhaus et al., 2008; Wilhelm et al., 2008). Although caution is required in drawing any conclusions about cause and effect in these cases, studies later in development have shown that restricting or optimising sleep durations have direct effects on memory abilities and academic outcomes (Curcio, Ferrara, & De Gennaro, 2006). Furthermore, treating physical sleep disrupting features, for example by removing tonsils and adenoids, improved school performance, whereas in a group who elected not to have any treatment, academic performance did not improve (Gozal, 1998). Therefore, sleep behaviours are implicated in memory and other cognitive outcomes, and should be taken into consideration when assessing these abilities.

7.1.3 Attention, executive function, and sleep in Down syndrome

7.1.3.1 Attention

Individuals with DS are more inattentive, distractible and hyperactive than their TD peers across development (Cuskelly & Dadds, 1992; Pueschel, 1990; Stores, Stores, Fellows, & Buckley, 1998). Sustained attention was MA-delayed in infancy matched on raw scores from the BSID-2 (J. H. Brown et al., 2003). However, by 7 to 16 years of age there was not a significant difference between DS and BPVS-matched TD controls in sustained attentional measures (Cornish, Scerif, & Karmiloff-Smith, 2007; Trezise, Gray, & Sheppard, 2008). Sustained attention was not impaired in participants with DS aged 11 to 19 years compared to logical operation-matched TD participants, although the DS group made more errors, indicating that although attention was maintained, rules were forgotten sooner than in the TD cases (Lanfranchi, Jerman, Dal Pont, Alberti, & Vianello, 2010). Sustained attention was also MA appropriate based on the WPPIS in a study of individuals aged 5 to 14 years, particularly in auditory assessments (Breckenridge, Braddick, Anker, Woodhouse, & Atkinson, 2013). However, contradictory to this sustained attention measures did not correlate with either MA or CA in a sample of 25 individuals with DS aged 7 to 16 years, matched with TD individuals on the BPVS (Cornish et al., 2007). Therefore, although sustained attention abilities may be MA appropriate from aged 5 to 19, it is possible they do not improve over this age range in the DS population, indicating maximum levels may have been achieved by age 5 years. It should be noted that there are different trajectories of sustained and selective attention in the DS population across childhood, suggesting the conversion from a 2- to 3-component model of attention does occur in people with DS (Cornish et al., 2007).

Children with DS have greater intra-individual variability in task engagement than TD children, inconsistently performing in and engaging with identical tasks even across short periods of time (Wishart & Duffy, 1990). This has negative implications for research by decreasing the possibility that the outcomes of assessments are valid representations of participants' abilities. Some authors suggest this inconsistency in behaviour is due to decreased sustained attention or motivation (Harter & Zigler, 1974; Kasari & Freeman, 2001). However, evidence suggests motivation is not significantly impaired in individuals with DS in either childhood or early adolescence (Gilmore & Cuskelly, 2011; Gilmore, Cuskelly, & Hayes, 2003). Therefore, reduced sustained attention capacity is a potential but unconfirmed cause for individual differences in task performance.

In terms of processing abilities, which are frequently cited as measures of attention distribution patterns, participants with DS are prone to biased global processing of tasks rather than local, detailed attentional focusing, for example, in responding to Navon stimuli (Bihrle, Bellugi, Delis, & Marks, 1989; Porter & Coltheart, 2006).

Attentional control is the ability to ignore unnecessary information, requiring inhibition and cognitive flexibility. Comparing 7 to 16-year-olds with DS to BPVS-matched control groups with either poor or good attentional control abilities, the DS group had impaired attention control overall (Munir, Cornish, & Wilding, 2000). Another study showed that the higher the attentional control demanded by a task, the worse individuals with DS aged 7 to 18 years performed compared to controls matched on logical operations (Lanfranchi et al., 2004). These findings indicate that attentional control is impaired throughout childhood and adolescence compared to MA-matched TD individuals. It is possible that this ability

is more affected than sustained attention due to the limited MA that is attained in the DS population. The greater impact on attentional control development may be because this is a more complex ability that is not observed in TD individuals until around 4 years and 6 months, thus if this MA is not attained in the participant with DS then attentional control abilities may not be fully developed (Breckenridge, Braddick, & Atkinson, 2013). Further work is needed to clarify the effect specific to "attentional control", and if this form of processing does indeed develop in individuals with DS.

7.1.3.2 Executive function

Studies of executive function in DS populations aged 11 to 19 years of age have shown all features excepting fluency (i.e. inhibition, planning, spatial WM) were impaired compared to DAS-matched TD individuals (Pennington et al., 2003). Comparing 10 to 19-year-olds with DS with SBAB-matched TD individuals, the DS group had impaired executive loaded verbal and visuospatial WM and set shifting abilities, but not impaired inhibition or fluency (Carney, Brown, & Henry, 2013). Another study comparing 10 to 19-year-olds with DS with receptive vocabulary-matched TD individuals showed prepotent response inhibition, resistance to proactive interference and response to distractor inhibition were all impaired in the DS group (Borella, Carretti, & Lanfranchi, 2013). A study of 11 to 19-year-olds with DS matched on logical operations with TD participants assessed inhibition, set shifting, conceptual shifting, and planning abilities, which were all impaired, but again fluency abilities were not delayed for MA (Lanfranchi et al., 2010). Therefore, the Carney et al., (2013) paper seems an outlier result where inhibition is not impaired, why this is not impaired in this single study is unclear. This result could be due to the sample, the MA-matching method, or the inhibition task itself,

however, other studies used similar paradigms, so further work is required to elucidate if inhibition is MA-delayed in the DS population.

Specific studies of inhibition in participants with DS aged 7 to 16 years showed there was a delay in inhibition abilities compared to BPVS-matched TD controls (Cornish et al., 2007). Response inhibition was impaired in both auditory and visual sustained attention tasks, but less evident in the auditory tasks in a group aged 10 to 21 with DS matched on K-BIT matrices (Faught, Conners, & Himmelberger, 2016). Therefore, the majority of studies conclude that all executive function measures, except fluency, are impaired for participants with DS aged 7 to 21 years compared to TD individuals, matched on various cognitive abilities. These results also suggest an uneven development of executive function in the DS population. It should be taken into consideration that semantic verbal fluency, as opposed to phonological, relies more on the temporal than frontal lobe (Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998). Therefore, this behaviour relies on different neural structures than other executive function measures, which may provide a structural basis for the asynchronous development between this and other, more frontal, measures. Assessments of central executive abilities have found impaired function in participants with DS compared to WPPIS matched TD individuals (Lanfranchi, Jerman, et al., 2009).

The brains of people with DS are characterised by proportionally decreased frontal, cerebellar, and temporal limbic volumes, compared to TD individuals, hippocampal volume specifically is also proportionally decreased (Jernigan et al., 1993; Onorati, Condoluci, Pierallini, Sarà, & Albertini, 2013). There is evidence of reduced volume of the rostral fifth of the corpus callosum, responsible for prefrontal connections, and thought to directly associate with verbal fluency

abilities, which requires coordination between the two lobes (Pinter, Eliez, Schmitt, Capone, & Reiss, 2001). Due to the reliance on the PFC for executive function abilities, and the well-characterised structural changes in the PFC seen in the DS population, it is possible that this is the direct structural cause of deficits seen in this cognitive domain (Case, 1992; Miyake et al., 2000; Raz et al., 1995). There is a moderate correlation between PFC measures and hippocampal measures in the DS population (Pennington et al., 2003), suggesting a functional and structural association between executive function and memory abilities. Given the atypical development of the structure thought to be responsible for verbal fluency, it is surprising that verbal fluency is the only measure of executive function that is not MA-delayed in the DS population. It is possible that other brain structures are compensating for this function, or that it is a relatively simple ability and thus able to function with reduced structural support.

Parent- and teacher-rated measures of executive function have high validity in the DS population aged 4 to 11 years (Edgin, Mason, et al., 2010). Planning, inhibition and WM were delayed, whereas emotional control and shifting were not, compared to TD controls matched on the Mullen Scales of Early Learning, DAS, or Leiter-R Brief IQ (Daunhauer et al., 2014; Lee et al., 2011). These findings imply that the development of cold components of executive function was more delayed in the DS population than hot module development. This is consistent with functional and structural studies that have shown in the DS population there is higher connectivity in the ventral than dorsal frontal regions of the brain (Pujol et al., 2015).

7.1.3.3 Sleep

Sleep disorders occur in at least 50% of individuals with DS (Breslin, Edgin, Bootzin, Goodwin, & Nadel, 2011; Carter, McCaughey, Annaz, & Hill, 2009; Quine,

1991). Obstructive sleep apnoea syndrome (OSAS) is seen in 45-65% of children with DS (Marcus, Keens, Bautista, von Pechmann, & Ward, 1991). OSAS is associated with significantly decreased verbal IQ (9 points lower than individuals without OSAS) and impaired cognitive flexibility, potentially via impaired PFC function (Beebe & Gozal, 2002; Breslin et al., 2014). There are also many behavioural sleep disorders associated with DS; delayed sleep onset and impaired sleep maintenance occur at high rates; bed-wetting is also more common and has a longer duration than in the TD population (Wood & Sacks, 2004). All disorders that negatively affect sleep or reduce oxygen flow increase the risk of hyperactivity, irritability, and aggression, whilst reducing concentration span, attention skills, and the ability to learn (Beebe et al., 2004; Blunden, Lushington, Lorenzen, Martin, & Kennedy, 2005). Thus, any disturbed sleep has negative results on child development and should be managed as early as possible. For the same reasons it is important to consider sleep quality and duration when assessing cognitive development.

Although there are not many studies of the effects of sleep quality on cognition in the DS population, a study on participants aged 7 to 12 years found OSAS was associated with significantly delayed set-shifting of executive function, but not attention, associative memory, non-verbal IQ or independent behaviour ratings (Breslin et al., 2014). A study of participants aged 14 to 31 years with DS found a significant association between OSAS ratings and BMI, and negative correlations with verbal fluency and set shifting abilities (Chen, Spanò, & Edgin, 2013). A study on toddlers with DS aged 27 to 64 months showed that impaired sleep abilities were associated with delayed language and vocabulary measures, independent behaviours, set-shifting, WM and planning (executive functions) but

not with delayed inhibition or emotional control (Edgin et al., 2015). Therefore, the effects of disturbed sleep on behavioural outcomes are variable, but generally appear to cause impairment across development.

7.1.4 The current study

The focus of this study is both the development of sustained attention and executive function abilities, as well as sleep. Sustained attentional measures in participants with DS from aged 5 onwards are appropriate for MA measures such as BPVS and logical operations, but have been reported to not develop in correlation with increasing MA or CA. The lack of correlation could be due to maximum levels being reached by age 5, and no further improvement in sustained attention abilities after this age, or due to the cross-sectional design. This study followed up those findings by assessing sustained attention over early and late childhood and comparing groups with DS to CA-matched TD participants to assess the change in sustained attention over development in a cross-sectional design. It was hypothesised that because of CA rather than MA matching sustained attention would be impaired in the DS group, and that the change in sustained attention over development would be significantly different between DS and CA-matched TD groups, due to the apparent lack of improvement in the DS group.

Executive function development was measured by the Gap-Overlap paradigm, a measure used in infancy and early childhood to assess executive function. This task assesses abilities through eye gaze, making it applicable to young ages, and yields three basic measures, baseline, gap, and overlap looking times, which are then converted to disengagement and facilitation measures. Event related potential (ERP) studies have shown evidence that these abilities rely on different neural structures. Disengagement is a measure of top-down attentional

control, reliant on the frontal lobe, that also requires strong parietal engagement (Csibra, Johnson, & Tucker, 1997). This parietal activation is seen in overlap trials prior to the disengagement-saccade, implying it is involved in inhibition and termination of fixation (Csibra et al., 1997). Therefore, both attentional control and inhibition are required for disengagement. Facilitation is a measure of cognitive flexibility derived from the increased speed in looking to the peripheral stimulus in the absence of a central stimulus. The less flexible visual attention abilities are, the smaller the facilitation effect will be (Fischer & Weber, 1993). Developmental disorders associated with reduced attentional abilities are associated with more saccades per second than in typical development (Kemner, Verbaten, Cuperus, Camfferman, & van Engeland, 1998). Adults with ID were slower at both gap and overlap conditions compared to CA-matched TD individuals, implying impaired disengagement and facilitation abilities compared to the TD group (Kawakubo et al., 2007). Overall, saccades that are more rapid than the TD group imply reduced sustained attention, whereas saccades slower than the TD group imply reduced attentional control and flexibility (Kawakubo, Maekawa, Itoh, Hashimoto, & Iwanami, 2004).

The ability to flexibly visually scan the environment, or not, is also referred to in the literature as a global vs. local processing preference (Freeseman, Colombo, & Coldren, 1993). Individuals with global processing preferences should have longer disengagement measures and those with local processing preferences should have shorter disengagement measures (Porter & Coltheart, 2006). The outcomes of disengagement and facilitation measures are therefore indicative of both executive functions abilities and processing preferences. In addition to this, propensity to disengage will also influence sustained attention measures, as those

less likely to disengage, or with longer fixation times, should also have better, or long, sustained attention behaviours.

Executive functions, with the exception of verbal fluency measures, all appear delayed in the DS population compared to TD participants matched on various cognitive abilities. However, all these assessments have relied on high-level cognitive control behavioural paradigms. Therefore, in this study executive function was assessed using eye-tracking, the lowest possible level of cognitive control. This paradigm required only eye gaze, and has been successfully used in TD infants. It was hypothesised that, due to the global processing preference of the DS population, disengagement would be significantly slower in the DS than TD populations. Facilitation, a measure of cognitive flexibility, was also hypothesised to be impaired overall. The current study also examined the change in both measures over developmental time to assess the trajectories of DS and TD development, without a specific hypothesis of impaired development.

Parental questionnaire measures of both attentional focusing and inhibitory control were correlated with experimental measures to validate the relationship between experimental and parental reported behaviours. Finally, data on the presence of SRBDs, as assessed by parental questionnaire, were collected and correlated with both attentional and executive function measures. It was hypothesised that there would be increased risk of SRBDs in the DS population compared to CA-matched TD participants, and that this increased risk would correlate with poorer sustained attention, facilitation and disengagement measures. Non-verbal and verbal score were also correlated with measures of sustained attention, disengagement and facilitation, to investigate associations between these measures.

7.2 Methods

7.2.1 Participants

Participants with and without DS were recruited as described in 2.2 Participants. Forty-three participants with DS were recruited between the ages of 4 and 14 years old. Thirty-two TD participants were recruited between the ages of 4 and 14 years old. Three participants with DS and two TD participants were excluded due to failure to attempt the eye-tracking tasks in this study. The number of participants for whom data were complete on each measure is outlined in Table 7.1.

Table 7.1 The mean and SD CA of all participants included in this analysis, and the N included in each assessment

	Early Childhood		Late Childhood	
	DS	TD	DS	TD
Mean CA in months (SD)	72.43 (20.57)	72.73 (17.77)	150.74 (22.24)	137.80 (18.04)
Overall N	21	15	19	15
Sustained Attention N	18	13	17	13
Disengagement N	16	14	14	15
Facilitation N	14	14	14	15
Inhibitory Control N	16	15	17	15
Attentional Focus N	16	14	17	15
SRBD N	14	14	16	15

7.2.2 Procedure

Sustained attention and executive function were assessed using the eye-tracking paradigms described below. The following parental report measures were also collected; these are described in detail in 2.4.4.3 Questionnaires. Non-verbal measures and verbal score were derived from pattern construction and the BPVS, which were administered as described in 2.4 Procedure.

7.2.2.1 Attention and inhibition experimental measures

Sustained attention was quantified as looking time to stimuli, and assessed by the familiarisation trials of the "memory for object" and "memory for object-in-place" paradigms, see 2.4.4.1 Eye-tracking. Initially four cartoon objects/animals were presented on the screen, matched on size, colour intensity, and familiarity. The images were presented in the corners of the screen for 8 seconds, their start size was 8° x 8°, they expanded and contracted to maintain attention. These objects were presented three times for 8 seconds, separated by a central stimulus to ensure individuals were looking at the centre of the screen at the start of each trial. These three stimuli exposures were displayed twice, with a gap of 20 seconds during which an engaging cartoon was presented. This resulted in 2 x (3 x 8 second) sessions of looking; these were summed over the six exposures for each individual, resulting in a measure of overall looking. The outcome variables were the total number of samples collected, and the number of valid samples. Therefore, the outcome was a "number of samples", rather than a measure of time. However, due to the positive linear relationship between sampling and time, it can be inferred that more valid samples in a trial correspond to longer a looking time. For this reason the outcome variables were referred to as "time" looking to the screen. Although previous work has referred to an early period of reactive attention lasting

a few seconds following stimulus presentation, this period of looking was not excluded herein as it still contributed to attention measures (Graziano et al., 2011; Richards, 1987). As the dependent variable was not of exact time but of relative time, no conclusions about the exact looking time could be made, only the relative numbers of valid samples between groups, age-groups, and individuals. Thus, sustained attention measures were calculated as below.

SUSTAINED ATTENTION = TOTAL_LOOKING (TRIAL_1+ TRIAL _2+ TRIAL _3+ TRIAL _4+ TRIAL _5+ TRIAL _6)

7.2.2.1.1 Gap-Overlap

Executive function was assessed with a Gap-overlap paradigm (Takagi, Frohman, & Zee, 1995). Gap-Overlap is a measure of visual attention components (Csibra et al., 1997). The task involves three trial types: baseline, gap and overlap, which are explained here. Trials were presented consecutively. Each trial began with a centrally presented cartoon (the central fixation stimulus) that expanded and contracted for 800 milliseconds in order to hold the participant's attention. In the baseline and gap trials, once the child fixated on the central stimulus, the central stimulus would remain on screen for 0-100 milliseconds and then disappear. On its disappearance, the target was immediately presented in the baseline trials and after a 200 milliseconds delay in the gap trials. In the overlap trials, the central stimulus would cease expanding, but remain on screen and overlap with the appearance of the target. The target was presented to either the left or the right of the central fixation stimulus at an eccentricity of 13°. It remained on screen until either the participant looked at it, or until 3 seconds had elapsed. If the participant looked at it within 1.2 seconds, they were rewarded by one of six animated cartoons.

These three conditions provide looking-time measures for a baseline, gap and overlap looking time. The baseline was subtracted from the overlap time to give a value of disengagement, the extra time taken to look at the peripheral stimuli if the central stimulus was on screen. The baseline was subtracted from the gap condition to give a measure of facilitation, the decrease in time taken to look to a peripheral stimuli if no central stimulus was on screen. Three stimuli types were used: central fixation, peripheral target, and reward. The central fixation stimulus was a colourful 8° x 8° animated cartoon of a clock. The peripheral target was an 8° x 8° cartoon of a cloud. The reward was one of six 8° x 8° animated cartoons (e.g., balloon, car, butterfly). All visual stimuli flickered and were accompanied by a nonverbal sound (*beep!* or *yip!*) to attract the participant's attention.

Trials were presented in blocks of 12 until 14 valid trials per condition were acquired or a maximum of 74 trials were presented. Trials were considered to be valid if the participant fixated on the target after 200 milliseconds and before 1.2 seconds of its appearance (Johnson, Posner, & Rothbart, 1991; Matsuzawa & Shimojo, 1997). In the overlap trials if the participant did not fixate on the peripheral target within this time window, then the trial was recorded as a failure to disengage. In addition, trials were considered invalid if the participant failed to look at the central stimulus prior to the presentation of the target or if the child blinked or looked away during the presentation of the stimulus. The whole procedure lasted around 5 minutes. The three conditions provide looking time measures for a baseline, gap and overlap looking time. The baseline was subtracted from the overlap time to give a value of "disengagement", the extra time taken to look at the peripheral stimuli if a central stimulus was on screen. The baseline was

subtracted from the gap condition to give a measure of "facilitation", the decrease in time taken to look to a peripheral stimulus if no central stimuli was on screen.

DISENGAGEMENT= OVERLAP- BASELINE

FACILITATION= GAP- BASELINE

7.2.2.2 Attention and inhibition questionnaire measures

Depending on the age of the participant the parent/carer filled out one of two behavioural temperament questionnaires. Parents of the early childhood group, aged 4 to 8 years, filled out the children's behaviour questionnaire (parent report), which consists of 195 questions on a Likert scale of 1 to 7, of "extremely untrue" to "extremely true" (Mary K Rothbart et al., 2001). This produces 15 sub-scale scores. The two used in this study were "Attentional focusing: Tendency to maintain attentional focus upon task-related channels" and "Inhibitory control: The capacity to plan and to suppress inappropriate approach responses under instructions or in novel or uncertain situations". Parents of the late childhood group, aged 10 to 14 years, were sent the Early Adolescent Temperament Questionnaires (parent report), this has 62 questions answered on a Likert scale 1-5 from "almost always untrue" to "almost always true" (L. K. Ellis & Rothbart, 2001). This produced 8 temperament scales, the two used in this study were "Attention: the capacity to focus attention as well as to shift attention when desired" and "Inhibitory control: the capacity to plan, and to suppress inappropriate responses". As individuals of the same age were administered the same questionnaires comparisons within age group are valid. Correlation analyses examine relationships between variables across age groups are also valid, as it is the relationship between

behavioural and parent-based variables that was being examined, not overall ability levels.

7.2.2.3 Sleep measures

The paediatric sleep questionnaire (PSQ) consists of a series of 73 yes/no questions probing medical issues that may affect sleep behaviours, and six questions rated on a 4-point scale from "does not apply" to "definitely applies most of the time". This questionnaire was normed on CA between 2:00 and 18:00, and so was used with all participants in this study. A subset of these questions (22) was used to calculate the risk in the child of a SRBD. If the outcome is 0.33 or higher then the child is at risk of a SRBD (Chervin et al., 2000).

7.2.3 Design

The study had both within and between group factors. Between groups were the participant groups of DS and TD and the age-groups of early and late childhood. Thus, the independent variables were group and age-group. There were multiple dependent variables listed in Table 7.2.

Table 7.2 The variables measured and the assessment they were derived from, along with the minimum and maximum scores possible or achieved

Task	Variable	Minimum	Maximum
Overlap	Time	0	845.89*
Gap	Time	0	638.29*
Baseline	Time	0	625.17*
Sustained Attention	Time	0	5400.00*
SRBD	Risk-questionnaire outcome	0	1
Attentional focusing from questionnaire	Ability-questionnaire outcome	0	30
Inhibitory control from questionnaire	Ability - questionnaire outcome	0	25

Note. *= No actual maximum, values represent maximum values achieved in the study

7.2.4 Analysis

Statistical analyses were carried out with IBM SPSS Statistics, Version 20 (IBM, 2011). Extraction of the desired measures from the overall eye-tracking data was carried out using MATLAB scripts (MathWorks, 2012). The outcome measure of the sustained attention paradigm is the validity of the samples, at a rate of

approximately 120 samples per second. Therefore, the outcome was a "number of samples", rather than a measure of time. However, due to the direct linear relationship between sampling and time, it can be inferred that more valid samples in a trial correspond to longer a looking time. The outcome of the Gap-Overlap task, which is analysed using formatted excel sheets, are reaction times in milliseconds.

7.3 Results

7.3.1 Characterisation of the population

The mean outcome measures of sustained attention, disengagement, and facilitation from eye-tracking paradigms, as well as the questionnaire outcomes measuring attentional focusing, inhibitory control, and SRBD risk are summarised in Table 7.3. In both early and late childhood groups ANOVAs were carried out on the variables, with group as the between subjects factor.

In the early childhood group there was not a significant difference between DS and CA-matched TD individuals in disengagement ($F(1,28)=1.03$, $p=0.326$, $\eta_p^2=0.057$), facilitation ($F(1,26)=1.07$, $p=0.315$, $\eta_p^2=0.059$), sustained attention ($F(1,29)=0.33$, $p=0.573$, $\eta_p^2=0.019$), attentional focusing ($F(1,28)=0.85$, $p=0.368$, $\eta_p^2=0.048$), or inhibitory control outcomes ($F(1,29)=0.00$, $p=0.996$, $\eta_p^2=0.000$), but there was a significant difference in SRBD risk ($F(1,26)=1.16$, $p=0.296$, $\eta_p^2=0.064$).

In the late childhood group there was not a significant difference in disengagement ($F(1,27)=0.01$, $p=0.966$, $\eta_p^2=0.000$) or facilitation outcomes ($F(1,27)=0.53$, $p=0.477$, $\eta_p^2=0.026$), but there were significant differences in sustained attention ($F(1,28)=10.34$, $p=0.004$, $\eta_p^2=0.341$), attentional focusing ($F(1,30)=26.74$, $p<0.001$, $\eta_p^2=0.572$), inhibitory control ($F(1,30)=13.45$, $p=0.002$, $\eta_p^2=0.402$) and SRBD risk outcomes ($F(1,29)=40.92$, $p<0.001$, $\eta_p^2=0.672$). Therefore, there were more significant differences between DS and TD groups in

late childhood than early childhood, demonstrating that the differences in attention, executive function, and sleep behaviours increased over developmental time.

Table 7.3 The mean and SD executive function experimental (milliseconds) and sustained attention experimental (N of samples), questionnaire based (ability score) and sleep measures (risk score), non-verbal and verbal measures of all participants included in this analysis

	Early Childhood		Late Childhood	
	DS	TD	DS	TD
Mean Sustained Attention	3774.00	4231.15	3557.29	4902.92
(SD)	(629.00)	(705.19)	(592.88)	(817.15)
Mean Disengagement	39	63	30	20
(SD)	(90)	(78)	(91)	(36)
Mean Facilitation	1	-28	-3	-35
(SD)	(55)	(34)	(94)	(21)
Mean Attentional Focusing	5.06	4.74	14.06	22.67
(SD)	(0.75)	(0.70)	(5.12)	(4.03)
Mean Inhibitory Control	4.77	4.67	13.47	19.33
(SD)	(0.95)	(0.89)	(5.00)	(3.31)
Mean SRBD	0.32	0.20	0.34	0.10
(SD)	(0.16)	(0.13)	(0.09)	(0.08)

Mean non-verbal raw score (SD)	8.83 (4.96)	26.87 (14.07)	16.00 (8.52)	40.60 (13.59)
N	6	15	10	15
Mean Verbal score (SD)	39.00 (17.68)	88.80 (21.51)	68.11 (17.34)	142.93 (14.70)
N	20	15	18	15

7.3.2 Sustained attention

A two-way ANOVA was conducted to examine the effect of age and group on sustained attention. There was a significant main effect of group, with the DS group looking less than the TD group ($F(1,57)=12.89$, $p=0.001$, $\eta_p^2=0.184$). There was not a significant difference effect of age on sustained attention ($F(1,57)=0.82$, $p=0.369$, $\eta_p^2=0.014$). There was not a significant interaction between group and age-group ($F(1,57)=3.13$, $p=0.082$, $\eta_p^2=0.052$), as shown in Figure 7.1.

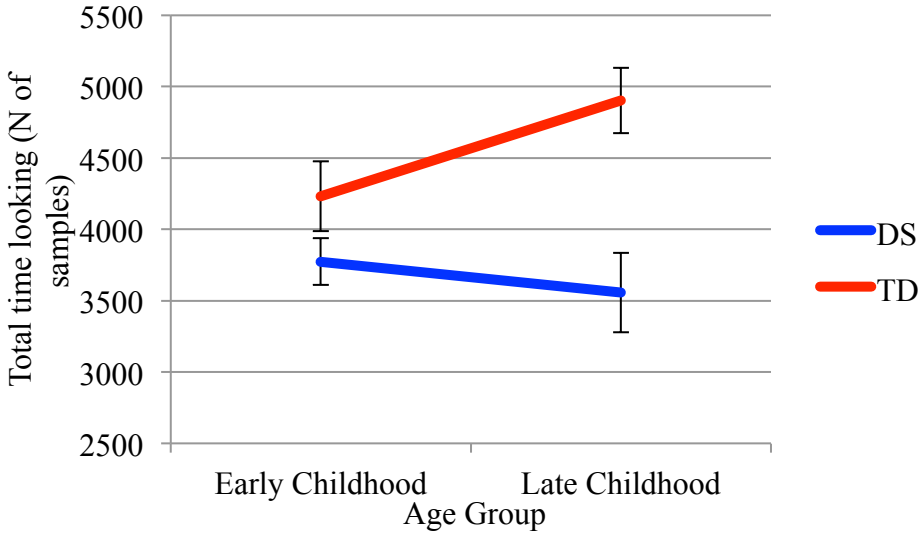

Figure 7.1 Mean total looking time over the 6 trials of the sustained attention measure in DS and TD groups over early and late childhood. Error bars represent +/- 1 SE

7.3.3 Gap-overlap dependent variables

Two-way ANOVAs were conducted to examine the effects of age and group on the baseline, disengagement and facilitation measures. If the results were significant, ANOVAs were also conducted within group or age group to examine the effect of either group or age on the variable.

7.3.3.1 Baseline

The baseline measure was significantly affected by group, the DS group were significantly impaired compared to the TD group, ($F(1,56)=9.31$, $p=0.003$, $\eta_p^2=0.142$). There was not a significant effect of age in baseline ($F(1,56)=1.79$, $p=0.186$, $\eta_p^2=0.031$). There was not a significant interaction between group and age-group ($F(1,56)=0.91$, $p=0.344$, $\eta_p^2=0.016$).

7.3.3.2 Disengagement

The disengagement measure was not significantly affected by group ($F(1,55)=0.14$, $p=0.712$, $\eta_p^2=0.003$). There was not a significant effect of age in

disengagement ($F(1,55)=1.60$, $p=0.211$, $\eta_p^2=0.028$). The change in disengagement was not significantly different between groups, ($F(1,55)=0.72$, $p=0.400$, $\eta_p^2=0.013$), as shown in Figure 7.2.

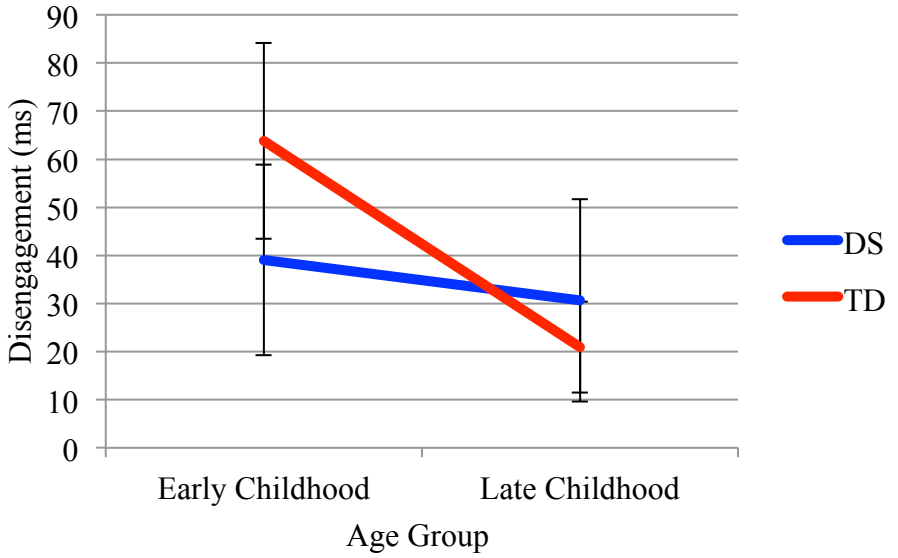

Figure 7.2 Mean disengagement in DS and TD groups over early and late childhood. Error bars represent +/- 1 SE

7.3.3.3 Facilitation

The facilitation measure was significantly different between groups ($F(1,53)=4.08$, $p=0.048$, $\eta_p^2=0.072$). There was not a significant difference in facilitation between early and late childhood ($F(1,53)=0.16$, $p=0.692$, $\eta_p^2=0.003$). There was not a significant interaction between group and age-group ($F(1,53)=0.001$, $p=0.970$, $\eta_p^2<0.001$), as shown in Figure 7.3.

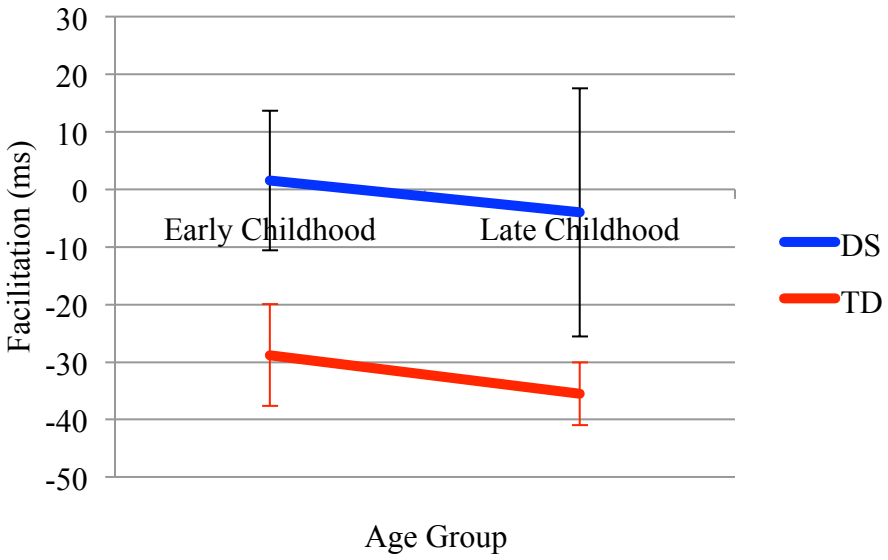

Figure 7.3 Mean facilitation in DS and TD groups over early and late childhood. Error bars represent +/- 1 SE

7.3.4 Correlations between experimental measures of sustained attention, disengagement, facilitation, and CA, questionnaire measures of attentional focusing, inhibitory control, SRBD, non-verbal and verbal scores.

To assess if the behaviours in sustained attention and inhibition experimental measures were associated with CA, parent reported measures of the same abilities, and risk of SRBD, correlation analyses were carried out and summarised in Table 7.4. Both disengagement and facilitation measures were included; therefore, both measures of cognitive flexibility and inhibition are correlated with questionnaire measures and risk of SRBDs. Non-verbal measures and verbal score are included to complement previous analyses and examine the synchronicity of the emergence of these abilities.

We first establish the observed relationships in the TD sample before comparing these to the DS population behaviours. In the TD group, CA positively correlated with sustained attention, meaning with increasing age participants had

longer attention spans. CA negatively correlated with disengagement; therefore, with increasing CA participants were faster at disengaging from the central stimuli. Disengagement significantly correlated with verbal score and non-verbal raw scores, demonstrating the association between these abilities in TD individuals. There was no significant correlation between facilitation or sustained attention and CA, non-verbal raw or verbal scores. The parental measure of attentional focusing positively correlated with the experimental measure of sustained attention, but was not significantly correlated with either measure of executive function. The parental measure of inhibitory control did not significantly correlate with any experimental task measures, suggesting the outcomes of the gap-overlap may tap different abilities than the parental-report questionnaire. Risk of SRBD negatively correlated with sustained attention, indicating that increased risk of SRBD was associated with reduced sustained attention abilities.

In the DS group, none of the measures significantly correlated. There was no significant correlation between CA and the experimental measures. This indicates that developmental time and life experience did not significantly affect sustained attention or disengagement abilities, as opposed to in the TD population. The observed correlations between parental-report attentional focusing and sustained attention measures was absent, indicating this relationship is weaker in the DS population than in the TD. The correlation between SRBD and sustained attention was also absent, suggesting increased SRBD does not affect participants with DS in the same way as TD participants. No measure significantly correlated with non-verbal raw or verbal scores, showing these abilities were not associated in the DS population.

Table 7.4 Correlation coefficients, significance and N's for sustained attention, disengagement and facilitation and CA, parental measures of attentional focusing, inhibitory control and risk of SRBD, and non-verbal raw score (derived from pattern construction) and verbal score (derived from BPVS). CA and MA in months

Group	Measure	Statistic	CA	Attentional Focusing	Inhibitory Control	SRBD	Non-verbal raw	Verbal score
DS	Sustained attention	Pearson Correlation	-0.094	-0.172	0.063	-0.042	0.010	0.16
		Sig. (2-tailed)	0.593	0.371	0.745	0.834	0.962	0.373
		N	35	29	29	27	26	33
	Disengagement	Pearson Correlation	0.028	0.001	-0.162	0.101	-0.253	0.021
		Sig. (2-tailed)	0.883	0.997	0.449	0.664	0.244	0.916
		N	30	24	24	21	23	29
	Facilitation	Pearson Correlation	0.019	0.164	0.125	0.254	-0.201	-0.009

		Sig. (2-tailed)	0.922	0.465	0.58	0.28	0.369	0.964
		N	28	22	22	20	22	27
TD	Sustained attention	Pearson Correlation	0.481*	0.488*	0.385	-0.420*	-0.225	0.364
		Sig. (2-tailed)	0.013	0.013	0.052	0.037	0.260	0.067
		N	26	25	26	25	27	26
	Disengagement	Pearson Correlation	-0.435*	-0.211	-0.299	-0.236	-0.582**	-0.570**
		Sig. (2-tailed)	0.018	0.281	0.115	0.227	0.001	0.001
		N	29	28	29	28	29	29
	Facilitation	Pearson Correlation	-0.195	-0.183	-0.15	0.374	0.008	-0.052
		Sig. (2-tailed)	0.312	0.352	0.436	0.050	0.965	0.787
		N	29	28	29	28	29	29

* p<0.05, ** p<0.001

7.4 Discussion

The primary hypothesis of this study was that sustained attention would be significantly impaired in the DS group overall, and development of sustained attention from early to late childhood would be significantly different between DS and TD groups. There was statistical support for the overall impairment in sustained attention with a small effect size, but development did not display a significant difference. However, when examining within age-groups there was a significant difference between sustained attention measures in late childhood that did not exist in early childhood with a large effect size. Therefore, although the interaction was only trending to significance, there is a significant difference in behaviours in late childhood between groups, suggesting development of sustained attention was not the same in TD and DS populations.

The second hypothesis was that disengagement would be impaired in the DS group overall. There was also a non-directional investigation of the development of disengagement and facilitation over early and late childhood between groups. The hypothesised impairment in disengagement was not present, suggesting that, although previous literature has found impairments in all executive function measures except verbal fluency, at low levels of cognitive control there is no significant difference between the TD and DS groups abilities to disengage from a central stimulus and re-orientate to the peripheral stimulus. This was an unexpected result due to the reported preference for global processing in the DS population, which should impair disengagement, therefore the relationship between processing and executive function may not be as simple as previously expected (Bihrle et al., 1989; Porter & Coltheart, 2006). Disengagement in the TD group improved with age, which has also been observed in previous studies of

infants and adults (Elsabbagh, Fernandes, Webb, Dawson, & Charman, 2013; Hood & Atkinson, 1993). Although disengagement was not significantly different between groups, facilitation was significantly impaired in the DS group, although the effect size was very small. This suggests that the DS group did not benefit from the time interval between central stimulus disappearance and peripheral stimulus presentation, to the same degree that the TD population do. This is in agreement with other literature suggesting people with DS do not benefit in the same way as TD individuals from features such as patterned data or verbal labels (Carretti et al., 2013; Laws, 2002). There was not a significant interaction between group and age-group in either facilitation or disengagement, suggesting that neither skill develop significantly differently between the two groups across childhood.

It was hypothesised that increased likelihood of SRBDs would correlate with poorer sustained attention and executive function measures. This would mean a negative correlation with sustained attention and disengagement and a positive correlation with facilitation. This was seen in the TD group although only the correlation with sustained attention reached significance, suggesting this ability may be more sensitive to interference from impaired sleep than executive function measures. In the DS group, there were no significant correlations, suggesting that likelihood of SRBDs did not significantly affect sustained attention, disengagement, or facilitation behaviours in the DS population.

The lack of significant correlation analyses in the DS group indicated that, although attentional and disengagement abilities improved with CA in the TD population, this correlation may not exist in the DS population. Therefore, increased experience and other features associated with CA, did not affect the development of these abilities in the DS population as in the TD population. These results agree

with the previously reported absence of a correlation between sustained attention and CA in the DS population (Cornish et al., 2007). However, it is always possible that this finding is an artefact, and a limitation, of using a cross-sectional design.

In the measure of sustained attention trending significance and Figure 7.1 suggested that, although in early childhood the groups did not appear significantly different, by late childhood the TD group had improved, whereas the DS group had not, resulting in a significant difference between sustained attentional abilities in the DS and TD groups in late childhood, with large effect size. In fact, the gradient of the DS group across childhood appears to be almost zero, indicating this ability does not improve over this developmental time period, agreeing with previous literature (Cornish et al., 2007). Therefore, it is not surprising that this measure did not correlate with CA. It is interesting that age did not significantly affect ability, suggesting that both groups may have reached near-adult levels of sustained attention ability by early childhood.

Disengagement, a measure of attentional control, or a combination of both attention and inhibition (Csibra et al., 1997), is illustrated in Figure 7.2. As this is a measure of the difference in reaction time taken to orient to a peripheral stimulus in the presence and absence of a central stimulus, the smaller this value, the quicker the participants were able to re-orient to the peripheral stimulus in the presence of a central stimulus. Interestingly, in early childhood the DS group were faster than the TD group. However, in late childhood, the TD group performed faster than DS group. Again, age did not significantly affect this ability suggesting it did not significantly improve across childhood. Faster disengagement times, as seen in the early childhood DS group, are associated with impaired sustained attention abilities (Kawakubo et al., 2004), a theoretical association that is supported by our results.

Facilitation, a measure of cognitive flexibility and visual attention (Fischer & Weber, 1993) calculated by the difference between baseline and gap measures, is illustrated in Figure 7.3. The more negative this value is the faster participants were orienting to a peripheral stimulus when there was a gap between the disappearance of a central stimulus and the presentation of the peripheral stimulus compared to when there was no gap between central stimulus disappearance and peripheral appearance. There was a significant effect of group, illustrating a significant impairment in facilitation in the DS population compared to CA-matched TD individuals. Again, the lack of age effect implies this ability may have gone through the most significant development prior to the CA range included in this study. Indeed, the majority of studies of the TD population utilising this task have examined infancy, although it is frequently used to study atypical adolescents and adults (Kawakubo et al., 2004; van der Geest, Kemner, Camfferman, Verbaten, & van Engeland, 2001).

In the TD group sustained attention and disengagement measures were significantly correlated with CA, but facilitation did not significantly improve over childhood in the TD population. This relationship between the executive functions of inhibition and cognitive flexibility is unexpected, as the literature has previously shown all executive functions except for inhibition correlated with CA (Lehto et al., 2003). This suggests that the relationship between executive functions and CA may be different at lower levels of control. The DS group gradient was almost flat in all three measures, illustrating why these measures did not correlate with CA.

The limitations of this study include the large standard error bars observed in both executive function measures. The wide range of abilities in both DS and TD populations suggest that these measures may be less specific than expected, or that

the development of these abilities across childhood are highly variable even within the TD population. The nature of the cognitive abilities being assessed also contributes to the difficulties in this study. Executive functions are less clearly defined into factorial-loaded functions in early development compared to adulthood, increasing the difficulty of identifying the exact features of attention and executive function assessed by the Gap-Overlap paradigm. Although disengagement requires inhibition of fixation, it could be argued that orientation or attentional control, rather than inhibition, is the major ability required for this behaviour. Therefore, the results of this study should be interpreted with caution, and whilst remembering the overlapping features of these abilities across development.

In conclusion, although there was no statistical evidence for different development of sustained attention between the DS and TD populations across childhood, by late childhood the difference between CA-matched groups was significant. This does not contradict previous literature which found sustained attention was not delayed for MA in individuals with DS aged 11 to 19, but advances these findings by showing that in the DS population in early childhood sustained attention is also CA appropriate. Low-level cognitive control executive function measures did not improve over development in the DS population, although again there was no statistical support for different trajectories of facilitation and disengagement development between the DS and TD populations across childhood. Disengagement was not significantly different between groups, but facilitation abilities were significantly impaired in the DS group, indicating reduced cognitive flexibility in the DS group compared to CA-matched TD individuals. The implications of these findings are that, although in the TD group these measures do improve marginally, said abilities may have already developed to such levels by

early childhood that further improvements are non-significant in both DS and TD groups.

Chapter 8 Trajectory analyses of memory measures

8.1 Introduction

The aim of this thesis was to examine the uneven development of memory abilities in individuals with DS. However, there are many ways of doing this theoretically. The preceding chapters have assessed experimental measures over two age-groups, early and late childhood, and compared the rates of development between groups over CA. However, these analyses were sometimes limited by small N's in sub groups caused by strict exclusion criteria for various tasks. Therefore, comparing the development of task abilities over the full range of CA could be more statistically meaningful than group by age-group comparisons. In addition to this, it would be interesting to examine the development of abilities within-formats in the DS group, to examine if different levels of cognitive control, or different storage systems, develop at different rates even within formats.

Previous literature has shown many measures to develop significantly slower in the DS population than in CA matched TD individuals. Therefore, it is also of interest to characterise the development of abilities across an appropriate MA-equivalent measure for the domain of the dependent variable. Comparing the trajectories across CA and MA-equivalent measures, can illustrate if the development of the ability is delayed across age, but in-line with other skills associated with that cognitive format. Comparing the difference in start points can illustrate if the youngest individuals are CA or MA appropriate for the ability. In this final experimental chapter, the aim is to apply a relatively new analytical approach to these data, to examine relationships between the development of the abilities assessed in this thesis. This method is presented in Thomas et al. (2009), and

enables the construction of developmental trajectories from cross-sectional data, as was collected here.

Previous studies have used this analytical method with the following outcomes. A comparison of holistic face recognition between participant groups with DS, WS and autism (split into low and high functioning) over CA and MA measures was carried out on individuals aged 3 to 13 years (Annaz et al., 2009). The analysis of face processing abilities across CA within groups highlighted the uneven nature of ability development in the DS group, which was not present in any other disorder group. The same ability trend was seen when comparisons were made over BPVS or pattern construction MA scores, indicating a genuine imbalance in development of holistic face processing abilities in the DS population that is unique to this syndrome. Another study assessed the development of motion processing ability in groups with and without autism aged 5 to 12 years, across CA, BPVS and pattern construction MA (Annaz et al., 2010). This revealed that sensitivity to biological motion did not develop in the group with autism over any measure, despite the fact that at the youngest CA and MA measures, the TD and autism group ability levels did not differ. Therefore, the methodology is appropriate for assessing the development of typical and atypical groups across the age ranges included in this study, and across the MA-equivalent measures included herein.

8.2 Methods

8.2.1 Participants

Participants with and without DS were recruited as described in Chapter 2. The nature of the trajectory analysis requires individuals in the TD group that match the lowest CA and MA in the DS group, for this reason an additional four younger TD individuals were assessed on all tasks included herein. Overall, the groups consisted of 43 participants with DS and 36 TD participants, with individual N per group and task shown in Table 8.1. Any tasks where performance was not significantly different from chance was removed, which excluded the object-in-place data. Individuals who were at floor or ceiling and outliers for any measure within the TD and DS groups were excluded from analyses; these exclusions are details in Table 8.1.

Table 8.1 N in each group that produced data for each memory assessment, including additional younger CA TD individuals

	DS			TD		
Memory or MA equivalent task	Original (N)	Excluding floor/ceiling scores (N)	Excluding outliers (N)	Original (N)	Excluding floor/ceiling scores (N)	Excluding outliers (N)
Object	33	33	33	28	28	28
Immediate spatial	24	16	16	36	24	24
Delayed spatial	24	10	10	36	28	28
Immediate Verbal	31	30	30	36	35	34
Delayed verbal	31	26	26	36	31	31
Immediate associative	35	35	35	29	29	28
Delayed associative	33	33	33	29	29	29
Pattern Construction	37	30	30	36	35	35
Verbal Score (BPVS)	41	41	41	36	36	36

8.2.2 Procedure

The tasks analysed in this chapter were presented and assessed as described in Chapter 2. Previous chapters have compared between age-groups and group overall ability levels, but the focus of this chapter is the change across the whole group. Therefore, the mean CA, non-verbal and verbal measures of each group that completed each task are summarised in Table 8.2.

Table 8.2 The mean CA, SD and range of the CA, non-verbal and verbal measures of each group that produced data for each task analysed in this section.

		CA		Non-verbal raw score		Verbal score	
Task	Measure	DS	TD	DS	TD	DS	TD
Total	Mean	110.07	97.69	11.23	31.74	52.73	109.64
	SD	20.87	21.91	7.51	16.59	21.89	36.44
	Range	45-175	31-167	34-70	34-189	12-106	40-160
Object memory	Mean	109.48	99.19	11.04	32.00	54.19	109.61
	SD	42.38	42.98	7.51	16.59	21.89	36.44
	Range	45-170	31-166	1-25	2-63	12-106	40-160
Verbal memory	Mean	119.77	97.69	11.04	31.03	55.60	106.67
	SD	39.13	43.13	7.51	16.59	21.89	36.44
	Range	47-175	31-167	1-25	2-63	12-106	40-160
Spatial memory	Mean	129.54	97.69	11.23	31.74	59.32	109.64
	SD	33.09	43.13	7.51	16.59	21.89	36.44
	Range	67-175	31-167	1-25	2-63	12-106	40-160
Immediate associative memory	Mean	110.20	94.80	12.04	31.74	65.88	109.64
	SD	42.84	43.9	7.51	16.59	21.89	36.44
	Range	45-170	31-166	1-25	2-63	12-106	40-160
Delayed associative memory	Mean	111.70	94.80	11.15	30.28	53.79	106.33
	SD	43.56	43.99	7.51	16.59	21.89	36.44
	Range	45-170	31-166	1-25	2-63	12-106	40-160

A correlation matrix was constructed within each sample to determine significant relationships between dependant variables and CA, non-verbal and verbal MA measures. Only variables with significant relationships with each measure in both groups were compared between groups. The outcomes of these analyses are presented in Table 8.3.

Table 8.3 A correlation matrix representing significant variances of each variable explained by CA, pattern construction raw scores and BPVS score

	CA		Pattern Construction raw		BPVS score	
	DS	TD	DS	TD	DS	TD
Immediate verbal	0.323	0.808**	0.440**	0.601**	0.356	0.707**
Delayed Verbal	0.422*	0.764**	0.751**	0.348	0.299	0.645**
Immediate Spatial	0.486	0.471*	0.560**	0.433**	0.294	0.516**
Delayed Spatial	0.085	0.399*	0.358	0.466*	-0.176	0.336
Digit Span	0.14	0.723**	0.256	0.493**	0.296	0.707**
Verbal Fluency	0.504**	0.828**	0.251	0.524**	0.566**	0.775**
Object memory	0.251	0.327	0.296	0.073	0.161	0.191
Immediate associative memory	0.089	0.274	0.145	0.249	-0.159	0.356
Delayed associative memory	0.387*	0.288	0.264	0.246	0.403*	0.117

*p<0.05, **p<0.001

Comparisons could only be made between a variable in two groups, and two variables in one group, where the predictor explained a significant proportion of the variance in both instances. The tasks were firstly analysed individually between groups across CA, if appropriate they were then compared between groups across an MA-equivalent measure. Due to the nature of comparing typical and atypical groups across any measure of MA, many of the TD individuals were not overlapping with the DS group. Comparisons were only carried out on those comparing only those individuals who overlapped for the MA-equivalent measure. Within the DS group, tasks assessing the same memory format were then compared across CA. The final analyses would compare tasks assessing the same memory format between groups over CA and overlapping MA. The outcome of this final analysis is if the relationships between the abilities are significantly different between groups. Although the comparison of visuospatial STM as measure by object memory eye-tracking, could have been compared with visuospatial WM and LTM from the BAS II task, it was not. The reason was the different levels of control these tasks required, it was deemed possible that this might complicate the interpretation of relationships between more appropriate comparison variables.

8.2.3 Design

The study had both within and between group factors. Between groups are the participant groups of DS and TD. Thus, the independent variable was group. Within groups are the measures of CA and MA equivalents. There are multiple dependent variables outlined in Table 8.4.

Table 8.4 The dependent variables measured in this chapter and the assessment they are derived from, along with the minimum and maximum scores possible or achieved

Task	Variable	Minimum	Maximum
Object memory	Average percentage looking time to target	0	100
Immediate verbal memory	N recalled over 3 immediate trials	0	60
Delayed verbal memory	N recalled	0	20
Immediate spatial memory	N recalled	0	20
Delayed spatial memory	N recalled	0	20
Immediate associative memory	Average percentage looking time to target	0	100
Delayed associative memory	Average percentage looking time to target	0	100
Pattern construction	Raw score	1	62
British Picture Vocabulary Scale	Verbal score	12	160

Note. Although some variables were measured in raw scores, when within or between group analyses involved comparing scores across multiple tasks, all scores were converted into percentages of maximum possible score

8.2.4 Analysis

All previously used data, as well as the data collected from four younger CA TD individuals, were collated. Eye-tracking measures of object, object-in-location, immediate and delayed associative memory outcomes were calculated as the average percentage looking time to target over the two test trials. Due to the lack of valid BPVS verbal MA measures derived from the DS population, verbal score, also calculated from the BPVS, was used as the verbal covariate in MA analyses, see 2.4.5.1.1 The British Picture Vocabulary Scale.

Analyses comparing the same behavioural tasks within or between groups used dependent variables as outlined in Table 8.4. Analysis comparing different behavioural tasks within or between groups were carried out on proportional values, by converting the scores to a percentage of the highest score recorded. Statistical analyses were carried out with IBM SPSS Statistics, Version 20 (IBM, 2011). For between group analyses, the dependent variable was entered in a Univariate General Linear Model, with group as the fixed factor. The adjusted CA or MA was then entered as the covariate. For within group analyses, the dependent variables were entered in a Multivariate General Linear Model, and the adjusted CA or MA was then entered as the covariate. For the between-group, between-task analyses, the dependent variables were entered in a Multivariate General Linear Model, group was entered as a fixed factor, and adjusted CA or MA equivalent was entered as covariate. Confidence intervals (95%) were calculated by regressing the dependent variable against either CA or MA measure.

Using the methods designed by Thomas et al. (2009), firstly the significance of variance explained by the model and the goodness of fit for each task were calculated. This analysis also provides data on the difference in performance at

onset, or the lowest CA assessed in the DS group, along with the interactions between CA and group task performance outcomes, and on the rates at which both groups improve. Depending on the results of these analyses and the presence of an appropriate covariate, each task was then assessed across an MA equivalent measure associated with the memory domain. Visuospatial measures were compared across pattern construction derived raw scores, and verbal abilities were compared across BPVS derived verbal score. Whenever the terminology 'MA measure' or 'MA equivalent' is used herein, it is these measures they are referring to. For the sake of brevity it is not repeated every time, but in any individual with an uneven cognitive profile, no single measure can truly represent 'MA'. Therefore, although these terms are used for clarity and succinctness, at no point is the author implying that any ability is actually associated with the composite mental ability of the individual or group. These analyses also yield results of goodness-of-fit, main and interaction effects of group and MA, performance disparity at onset, or the lowest MA assessed in the DS group, and the rates of improvement in each group. Due to the fact that the majority of our experimental measures do not yield MA data, the performance disparity at onset must be interpreted, not as MA difference, but difference in ability or performance in a particular task.

When comparing performance at onset it is desirable to compare the groups at the youngest CA or MA included in the DS group, rather than at CA or MA 0, which was not measured. To enable this, variables were adjusted by subtracting the youngest DS CA or MA equivalent value from all participants' respective CA or MA values (M. S. C. Thomas et al., 2009). Overall, CA and verbal and non-verbal abilities were calculated as below, however, within tasks if the youngest MA or CA varied, the calculation was altered to compensate for that.

CA= CA - 45

VERBAL MA EQUIVALENT= VERBAL SCORE - 12

SPATIAL MA EQUIVALENT = PATTERN CONSTRUCTION RAW - 1

The limited MA development of the DS group means only a subsection of the TD group fall within this range, which is why the N in the TD groups are smaller than in the initial sample. The N and mean CA of the DS and TD groups in these more restricted analyses are presented in Table 8.5.

Table 8.5 Mean, standard deviation and N in DS and TD groups in non-verbal and verbal measures including only overlapping scores

	Pattern Construction raw score "MA equivalent"		Verbal score "MA equivalent"	
	DS	TD	DS	TD
Mean score	11.23	13.33	52.73	76.59
(SD)	(7.51)	(7.95)	(21.89)	(19.49)
N	30	12	41	17

In addition to comparing the intercept and gradients of linear trajectories, analyses also provided a measure of goodness of fit of the model, and a significance

measure of the variance explained by the model. Differentiating between the dependent variables as either eye-tracking or behavioural measures, interpreting difference at the youngest CA or MA should be carried out as follows. As the eye-tracking measures are percentage based outcomes, these values are quoted when discussing performance at youngest CA or MA, whereas when analysing the behavioural tasks, and if appropriate, the difference in raw scores is provided. These raw scores are the 'number correctly recalled' in each behavioural assessment, but for the sake of brevity are referred to as 'points' hereafter. For clarity, when these results are fractions they will be rounded to the nearest whole number. Therefore, the disparity at onset is either referred to as a percentage when discussing eye-tracking or between task comparisons, or in points when discussing raw behavioural scores.

8.3 Results

8.3.1 Between group comparisons of two developmental trajectories

In this section, trajectories of delayed verbal and verbal fluency are compared between DS and TD groups over CA. Variables that had significant relationships with an appropriate MA measure in both groups are also compared across the restricted N of only those with overlapping scores on the MA equivalent measure. For the sake of full characterisation non-significant comparisons were also examined over CA and MA-appropriate measures, and included in Appendix C.

8.3.1.1 Visuospatial memory

8.3.1.1.1 Immediate spatial memory

When comparing only those with overlapping raw scores, the results are as follows. The goodness of fit was low (R^2=0.291). The two groups task outcomes did not develop at significantly different rates over MA, $F(1,21)=0.01$, $p=0.929$, $\eta_p^2<0.001$. There was not a significant difference at onset, $F(1,21)=0.04$, $p=0.851$, $\eta_p^2=0.002$, although immediate spatial recall was significantly modulated by MA, $F(1,21)=7.26$, $p=0.014$, $\eta_p^2=0.257$, as shown in Figure 8.1.

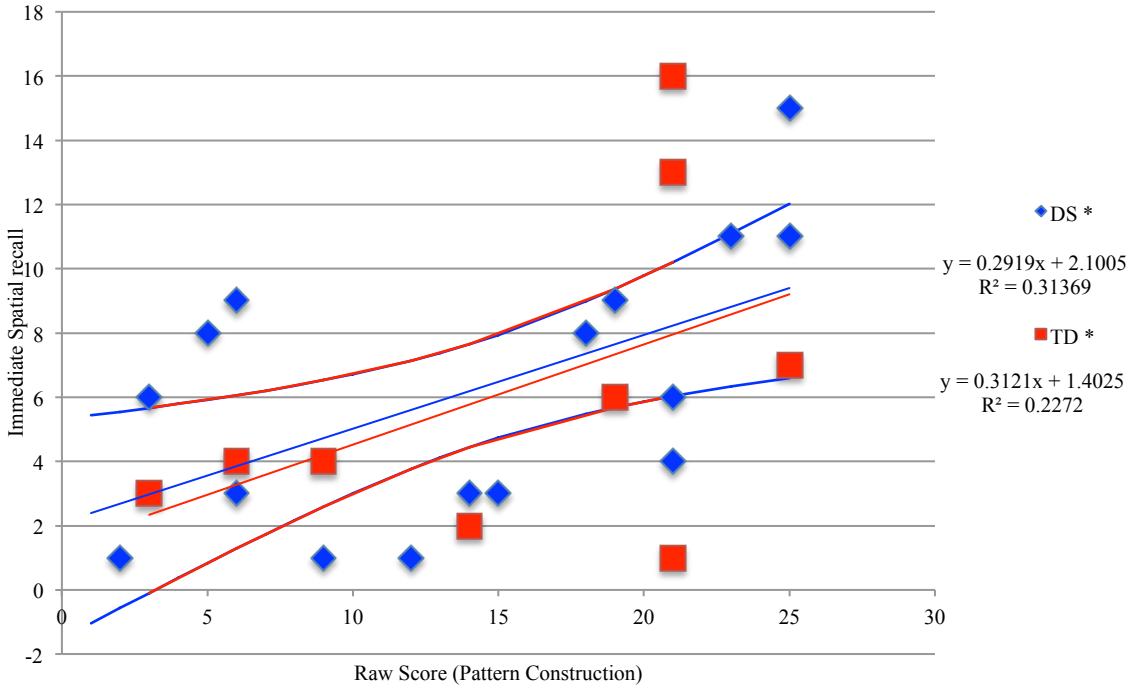

Figure 8.1 Immediate spatial recall over non-verbal raw score, calculated from pattern construction, in DS and TD groups, CI represents 95%

8.3.1.2 Verbal memory

8.3.1.2.1 Delayed verbal memory

The goodness of fit of this model was considerable (R^2=0.660) and explained a significant amount of the variance observed in this task, $F(3,48)=34.29$, $p<0.001$, $\eta_p^2=0.660$. The two groups did not improve significantly differently across CA in their delayed verbal recall abilities, $F(1,48)=0.68$, $p=0.413$, $\eta_p^2=0.0.014$. The performance at youngest CA assessed was significantly different between groups, $F(1,48)=10.71$, $p=0.002$, $\eta_p^2=0.182$. With the groups combined, CA significantly modulated performance on this task $F(1,48)=17.74$, $p<0.001$, $\eta_p^2=0.270$, as shown in Figure 8.2.

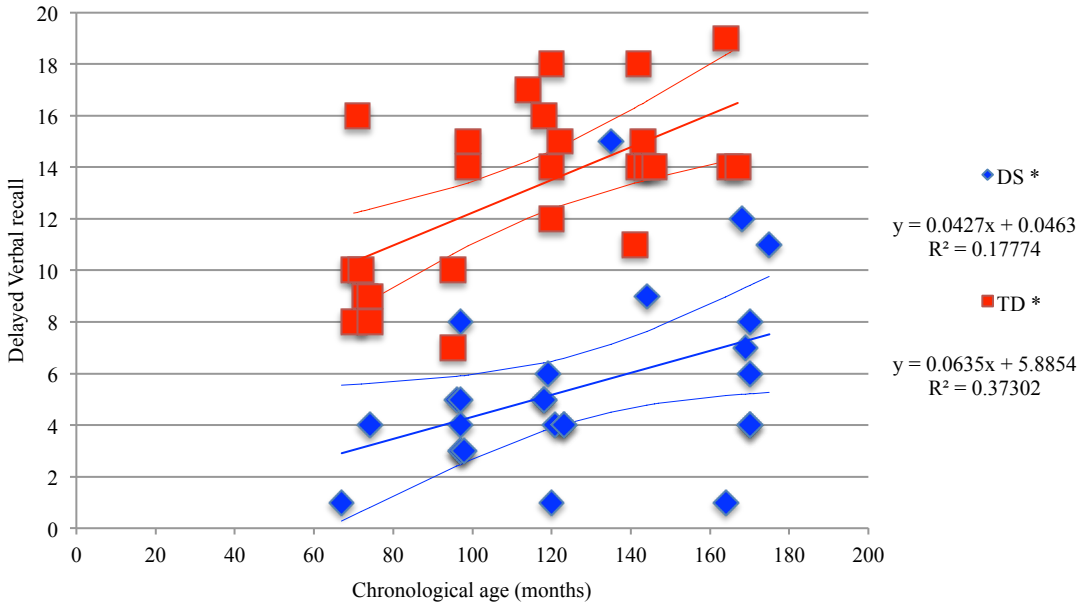

Figure 8.2 Delayed verbal recall over CA in DS and TD groups, CI represents 95%

8.3.1.2.2 Verbal Fluency

The goodness of fit of this model was considerable (R^2=0.738) and explained a significant proportion of the variance observed, $F(3,69)=64.73$, $p<0.001$, $\eta_p^2=0.738$. The performance at youngest CA assessed was not significantly different between groups, $F(1,69)=2.79$, $p=0.099$, $\eta_p^2=0.039$. With the groups combined, CA significantly affected performance on this task, $F(1,69)=81.71$, $p<0.001$, $\eta_p^2=0.542$. However, this should be interpreted with caution as there was also a significant interaction between CA and performance on this task between groups, $F(1,69)=31.10$, $p<0.001$, $\eta_p^2=0.311$. The DS group improved at a quarter of the rate of the TD group, as shown in Figure 8.3.

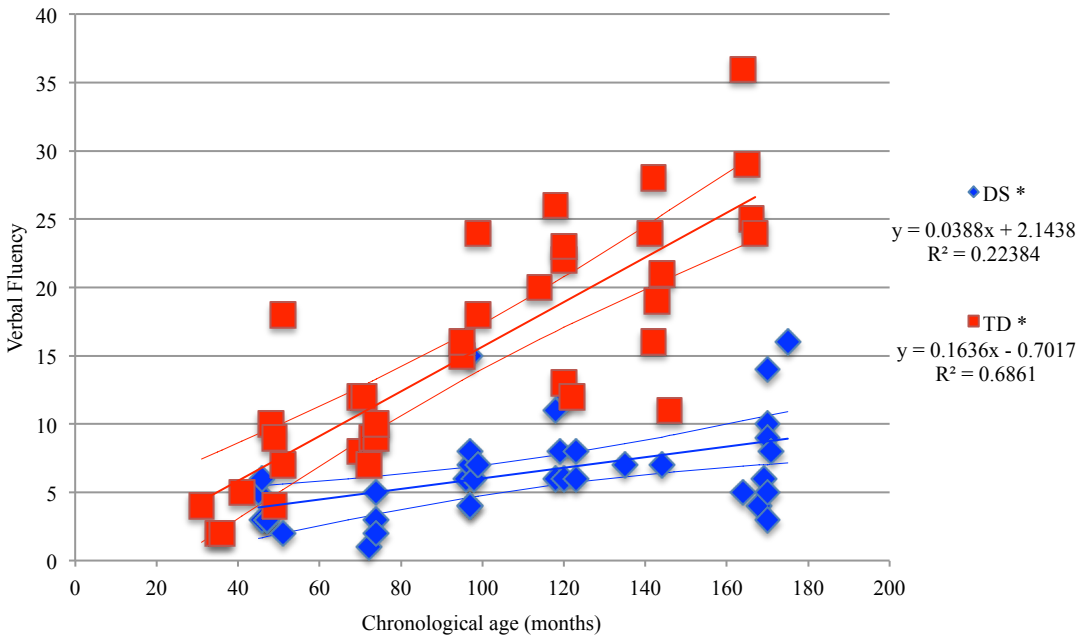

Figure 8.3 Verbal fluency over CA in DS and TD groups, CI represents 95%

Examining performance over verbal score and using only TD participants who fall within the same range of distributions as the DS group, the results were as follows. The goodness of fit of the model was medium (R^2=0.335). Group did not significantly alter performance at onset, F(1,41)=0.97, p=0.332, η_p^2=0.023. MA significantly modulated task performance across groups, F(1,41)=15.52, p<0.001, η_p^2=0.275. The relationship between verbal fluency and verbal score was not significantly different in the two groups, F(1,41)=1.39, p=0.246, η_p^2=0.033, as shown in Figure 8.4.

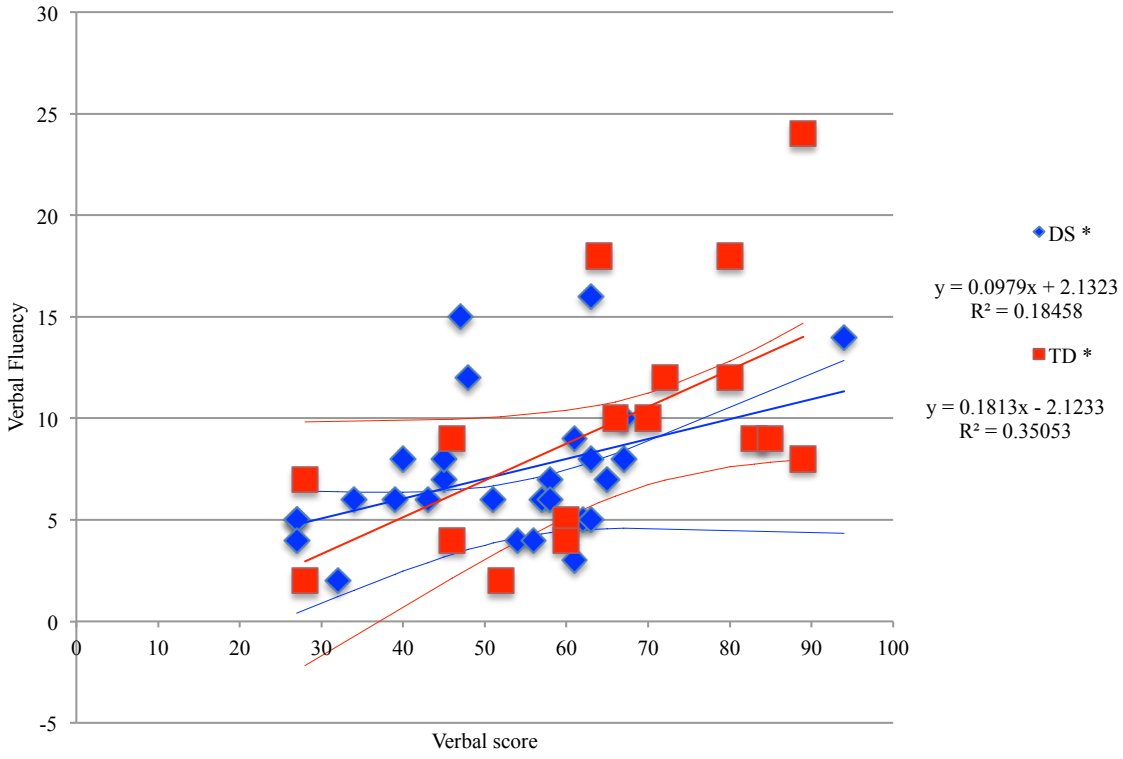

Figure 8.4 Verbal fluency over verbal score in DS and TD groups, CI represent 95%

8.3.2 Within group within format task comparisons

In this section, tasks assessing abilities within memory formats are compared within the DS group over CA. The only variables that were significantly explained by CA were delayed verbal recall and verbal fluency. Delayed associative memory was also explained, but as this is not verbal, its development is not analysed in this section.

8.3.2.1 Verbal memory

The DS group did not perform significantly differently on delayed verbal recall and verbal fluency, $F(1,23)=0.53$, $p=0.474$, $\eta_p^2=0.022$. CA did not significantly affect performance at onset ($F(1,23)=3.84$, $p=0.062$, $\eta_p^2=0.143$). There was not a significant interaction between task performance and CA ($F(1,23)=2.71$, $p=0.113$, $\eta_p^2=0.105$, implying the task abilities improved similarly with age, as shown in Figure 8.5.

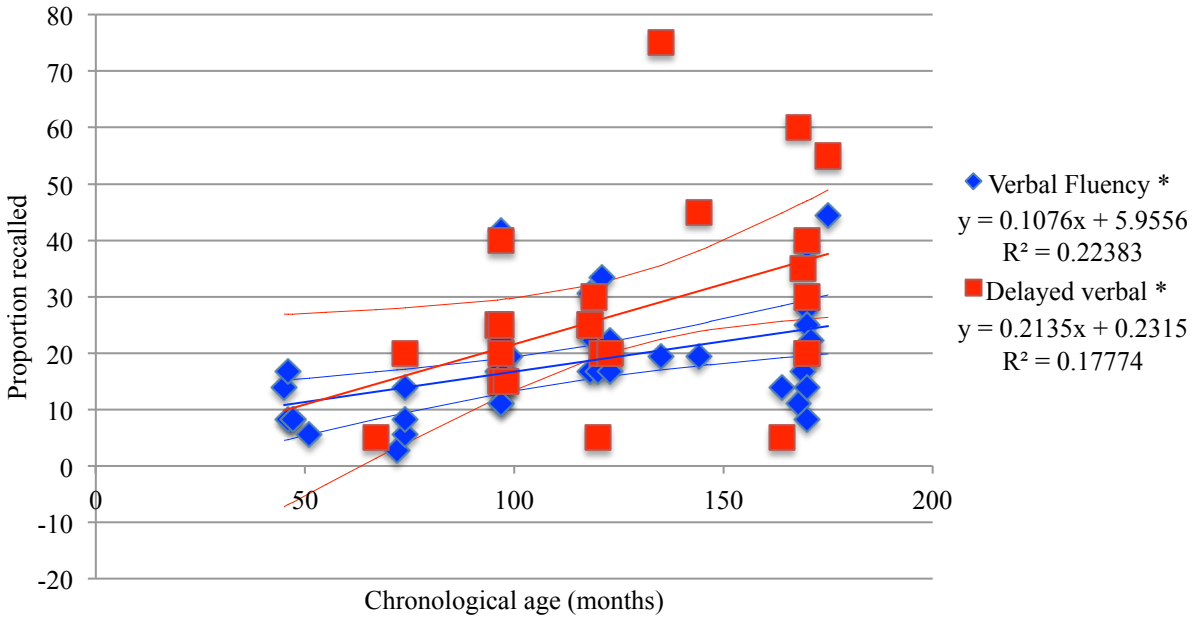

Figure 8.5 Delayed verbal memory and verbal fluency over CA in the DS group, CI represents 95%

8.4 Discussion

The aims of this chapter were to compare trajectories of within-format variable development both within and between groups, and if possible to compare development of multiple variables between groups in single analyses. Unfortunately, the latter aim was not achieved, as there were no cases where multiple within-format variables had significant variance explained by CA, or a domain appropriate measure.

The results of the trajectory analyses in this chapter suggest multiple findings of interest. Spatial WM development, although not CA appropriate in many studies, occurred at a comparable rate to the TD group across a visuospatial MA-equivalent measure. This suggests that visuospatial WM develops in-line with other, more general, spatial processing abilities measure by pattern construction. This finding further hints at an asynchrony between visuospatial WM and LTM development, even when measured across other within-format cognitive abilities.

In verbal abilities, verbal LTM, although significantly different at the youngest CA assessed, developed at comparable rates in the DS and TD groups. Verbal WM was not significantly explained by CA in the DS group and so this comparison could not be made, suggesting the frequently cited impaired verbal MW function is consistent across CA, whereas the delay noted in verbal LTM is capable of improving. The findings in verbal fluency contrasted with the LTM results. In verbal fluency, although performance at the youngest CA was not significantly different, the development of these abilities was significantly different between groups across CA, with a medium effect size. This suggests that verbal LTM and verbal fluency rely on different cognitive features. Verbal fluency development could also be compared across a within-format measure, verbal score. Here,

although both groups significantly improved across the measure, there was no difference between the rates of change between groups across verbal score. This suggests that verbal fluency, although delayed across CA development, develops in-line with other within-format abilities.

Within the DS group, the only two within-format abilities that could be compared across CA were verbal LTM and verbal fluency. There was not a significant difference between the development of these two abilities across CA within the DS group. This is a potentially confusing finding, considering verbal LTM developed comparable to TD individuals across CA, whereas verbal development was delayed. However, this is because when comparing two tasks-either within or between groups- because of the different outcomes, all measures have to be converted to percentages of the maximum score, either possible or achieved. Therefore, although in its raw form at development of verbal fluency abilities may be delayed compared to TD controls, comparing the relative rates of categorical verbal recall across development showed no significant difference in the DS group.

There are some limitations to the analysis carried out in this chapter. For example, the lack of sensitivity of some developmental measures, which had high levels of performance at floor, such as in visuospatial WM. As was briefly discussed this can affect both the difference in trajectories and in performance at onset. Floor performances flatten the gradient of the trajectory. If it were possible for individuals' true ability levels to be represented, which in these cases would appear negative, it is possible the gradient of the trajectories would no longer be significantly different, but the performance at youngest CA or MA would be. This is a hazard of applying standardised tasks to an atypical population. It does not invalidate the method, but it does mean that caution must be used in interpreting

outcomes. For this reason those at floor or ceiling were excluded from analysis, which reduced the N greatly. More sensitive tasks are needed to enable characterisation of the DS population more fully. A further limitation of this analysis, although inevitable to its nature, is the failure to consider individual differences and variability across tasks. This would be an interesting future study, but was not the aim of this investigation.

A limitation of this chapter was the smaller number of individuals included when analysing only overlapping scores on the MA-equivalents. Further to this it is unclear if these measures are the best measures of verbal and non-verbal abilities for the DS population. Although they are both popular and frequently used there were some obvious issues. For example, due to the frequency of floor scores in the BPVS MA, herein the actual measure used was a verbal score, subtracting the number of errors from the ceiling item achieved. This could potentially have inflated the scores achieved in the DS group by including individuals who would have otherwise been at or below floor, but was deemed worth doing as it provided more data than in the alternative situation. Overall, any so-called MA measure in a condition known for its uneven development is a potential limitation, but these measures are frequently used and thus were not inappropriate. A better method would be to have multiple measures of each format, perhaps at different cognitive load levels, but this risks having a protocol that is too long and reduces the meaningfulness of any data collected.

Considering the results in Table 8.3 the results can be discussed across CA and MA. Across CA, only two verbal memory measures, and a low-control measure of associative LTM improved in the DS group, whereas in the TD group, all verbal and spatial measures improved, and only low-control variables did not, potentially

due to the fact that the abilities required for these skills were already mostly matured by early childhood.

Across MA equivalent measures, in both the DS and TD groups, visuospatial abilities predicted more variability than the verbal MA equivalent, suggesting that overall visuospatial processing is more indicative of general cognitive abilities than verbal score. Verbal and visuospatial WM were significantly predicted by pattern construction MA, but not by CA, in the DS group. This suggests a discrepancy between the development of pattern construction ability development and CA, and also that both the visuospatial sketchpad and phonological loop development are associated with visuospatial processing, but not receptive language abilities. In the TD population, all variables are significantly associated, highlighting the uneven cognitive development of cognition in people with DS.

Overall, spatial WM and verbal fluency developed at appropriate rates for within-format MA equivalent measures in the DS group. The development of verbal fluency was delayed across CA, whereas verbal LTM developed at CA appropriate rates in the DS group. The comparable behaviours of verbal LTM and verbal fluency, suggests the development of these abilities may be associated.

Chapter 9 Discussion

Finally, bringing together all the empirical data presented in this thesis, the key questions raised in the introduction can be addressed. An initial problem identified within the literature was a tendency to compare groups with large CA ranges matched on single MA measures, and to exclude those with more severe disabilities or of younger CA. This thesis successfully assessed multiple memory domains at low CA and physical ability levels, and compared the development of these abilities between two narrow-ranged age-groups. The novel findings are first discussed in terms of verbal and visuospatial literature from the introduction, addressing gaps in the literature and ways in which these results advance our understanding. The benefits of low-control methodology and outcomes of these tasks are then discussed. The uneven cognitive profile of memory in DS is then outlined, and the reasons behind it are conjectured upon. Relationships between the results, mouse model results and Alzheimer's disease are briefly recapped, before outlining limitations and potential future work. The implications, and conclusions of this study are then presented.

9.1 Verbal memory

Previous studies of verbal memory in children with DS have reported that individuals were at floor aged 6, and although they improved across age 7 and 8 years, the delay compared to the block-design-matched TD group increased over time (Naess et al., 2015). The hypothesis was that verbal WM would develop at comparable rates to TD individuals. However, analysis showed that verbal WM development was delayed, supporting the previous findings of increasing delay (Chapman et al., 1991).

Another study of individuals aged 7 to 18 showed that the DS group performance on visually input and verbally output assessments, comparable to the assessment of verbal WM used herein, was delayed compared to WISC matched individuals, but not a BPVS matched group (Duarte et al., 2011). However, two further studies matched on PPVT-R and BPVS showed impaired verbal WM performance in the DS group (CA=8-20) compared to the control groups (Jarrold et al., 2002; Lanfranchi, Jerman, et al., 2009). The hypothesis of this study was that verbal WM would be impaired for verbal score. In this study the participants were younger CA (4-14) and the BPVS measure was slightly different, using verbal score rather than MA. Although the verbal score explained significant variance in the TD group, it did not in the DS group, suggesting development of WM was not comparable in individuals with DS compared to the TD group. This agrees with the findings of the latter studies, and extended the applicability of these findings to younger CA individuals.

Studies have suggested that both TD and DS groups switch to preferential visual encoding around MA 5 derived from logical operations (Lanfranchi et al., 2014). In the TD population, the conversion from visuospatial to verbal encoding and storage of data happens around MA 7 years. Although this study did not compare encoding techniques across MA, interpreting the results of overall abilities in comparable tasks did suggest that across all CA included in the study the DS group encoded verbal stimuli in a more visual manner than the TD group, see 4.3.9 Spatial distribution and verbal recall. Given that the verbal score is not an “MA”, the mean MA of this sample as calculated from pattern construction was 4:06, which means the finding of preferential visual encoding is in accordance with the TD theory of memory development, and advances prior findings by suggesting that

visual preference for verbal encoding may have a younger onset than previously found in the DS population.

A study of 14 individuals with mean CA 13:11 found an effect of recency but not primacy in verbal WM (Jarrold et al., 2000). Whereas both primacy and recency were observed in verbal LTM a group of participants with DS mean CA=16:07 (Carlesimo et al., 1997). In this study recency effects in WM developed similarly between DS and TD groups over childhood, whereas in LTM both recency and primacy developed similarly between groups. This advances the field by illustrating not only that these effects were present, but also that the rates of development across childhood of these abilities was similar to CA-matched TD individuals.

Rates of learning of verbal information were not significantly different between 15 individuals with DS (CA=16:07), and WISC or WAIS matched TD individuals (Carlesimo et al., 1997). The rates of learning between early and late childhood were different between DS and CA-matched TD individuals in this study, showing that although rates of learning are MA-appropriate, they were delayed for CA. However, the change in rates of learning over childhood were not significantly different, suggesting the development of this ability may be a good target for intervention.

Other studies have found no significant difference in rates of decay in a sample of individuals with DS, mean CA=20, compared to RPCM-matched TD individuals, or in a younger CA group matched on WISC or WAIS (Carlesimo et al., 1997; Purser & Jarrold, 2005). The change in decay across childhood was different between DS and TD groups, showing that similar to learning, decay was MA-appropriate but impaired for CA. This analysis also showed that the change in decay

across early and late childhood was not significantly different between groups, as in learning.

9.2 Visuospatial memory

Visuospatial WM abilities in the DS group improved between age 4 and adulthood (Couzens et al., 2011). The hypothesis was that visuospatial WM would improve at comparable rates to TD individuals, which was supported by the results.

Increasing the control required for the visuospatial WM task increased the impairment observed in the DS group compared to controls (Lanfranchi et al., 2012, 2004, 2015; Lanfranchi, Jerman, et al., 2009), as does moving from STM or WM to LTM storage modes (Visu-Petra et al., 2007). In this study the effect sizes of group on variables increases from STM to WM to LTM. Therefore, although the development of these abilities were not directly compared these results support previous literature, and advance them by showing the findings are also applicable at younger ages than previously examined. The uneven development of visuospatial memory abilities across childhood is a novel finding in DS cognition, and indicates encoding/retrieval function is more impaired than sketchpad function in this memory domain.

Visuospatial WM abilities were impaired in individuals aged 7 to 18 compared to WISC or WAIS matched, but not PPVT-R matched, TD participants, suggesting that visuospatial WM developed in-line with verbal abilities but not overall cognitive measures (Duarte et al., 2011). However, visuospatial WM was not impaired at onset or over trajectory of z-scores between DS aged 10 to 21 and ABIQ-matched TD participants (Carney, Henry, et al., 2013). Therefore, controlling for the distribution of group performances made the abilities appear appropriate for overall cognitive measures. The development of visuospatial WM abilities were

not different to TD individuals matched on pattern construction raw scores, showing that these abilities were developing at within-format appropriate rates. This advances previous findings by showing that, although impaired at onset, the development of visuospatial WM was in-line within other spatial processing skills in the DS population, and not delayed compared to pattern construction matched controls.

Previous studies have shown that although visuospatial memory abilities were not impaired at low MA, at higher MA the DS group were delayed compared to K-ABC matched TD individuals (Frenkel & Bourdin, 2009). The results of this study showed that when matched on a within-format measure, the DS group improved faster than the TD group, which is a novel finding. Visual WM abilities were impaired whereas spatial abilities were not in a group CA 10-30 matched on SBIS (Vicari et al., 2005). The only purely visual task here was the STM assessment, where the group effect was significant, although developed at a similar rate, showing that even at lower levels of control visual memory function impairment is observed in the DS group.

In a study of 12 individuals with DS with a mean CA of 20 years, there was no evidence for increased decay of visuospatial information compared to RCPM matched TD individuals (Purser & Jarrold, 2005). It was hypothesised that the decay of memory from WM to LTM would not develop differently between groups, the results supported this hypothesis. Therefore, this feature developed at a CA-appropriate rate in the DS group. In TD individuals the items assessed first were best recalled in visuospatial WM assessments (Hitch et al., 1988; Pickering et al., 1998). The effects of recency and primacy were measured, and both developed comparably to the CA-match TD group in WM and LTM assessments. Therefore, the

encoding mechanisms of visuospatial information appear to develop comparably between groups across childhood.

9.3 Low control tasks

The thesis aimed to include younger CA individuals, and those with more severe ID, by using low control tasks to assess visuospatial STM, associative STM and LTM, as well as measures of executive function and sustained attention. These tasks were successful in including more participants than some of the more complex behavioural tasks, illustrating the benefits of eye-tracking as a methodology. However, due to the previously discussed limitations of some tasks, it cannot be claimed that they were all successful in measuring memory abilities.

Previous studies of associative abilities have focussed on visual-spatial associative memory; therefore this was a novel investigation of between-format associative memory abilities at low levels of cognitive control. Previous studies of participants with DS aged 7-38 had showed impaired associative memory abilities (Edgin, Mason, et al., 2010; Visu-Petra et al., 2007). These results were supported herein as in both STM and LTM the DS group looked significantly less to the target area; showing even at low-control associative recognition was overall impaired in the DS population in childhood. However, this study did show that LTM was similar between groups in late childhood, demonstrating the importance of considering subset of the population, rather than averaging over large groups, and demonstrating between-format associative LTM as a relative strength in late childhood.

Eye-tracking was also used to assess measures of executive function and sustained attention. Sustained attention was hypothesised to be impaired for CA, as previous studies had found it to be MA-appropriate (Breckenridge, Braddick, Anker,

et al., 2013; Cornish et al., 2007; Trezise et al., 2008). This study added to previous findings by showing that sustained attention was impaired in both early and late childhood, and did not improve across CA, agreeing with outcomes observed in older individuals (Cornish et al., 2007).

Executive function was measured by the Gap-overlap paradigm, which had not been used in the DS population previously. Previous studies of executive functions in the DS population found all abilities were impaired, excepting fluency (Borella et al., 2013; Lanfranchi et al., 2010; Pennington et al., 2003). Therefore, the hypotheses were that both measures of the gap-overlap would be impaired. However, the results showed that at low-control levels although facilitation was impaired, disengagement was not. Therefore, although flexibility in cognition and scanning was impaired, top-down attentional control and inhibition abilities were not overall impaired in DS across childhood.

9.4 The uneven profile and how it is explained

The uneven profile of abilities overall and across development is presented in Table 9.1. Although not all calculations could be carried out herein, due to the strict inclusion criteria in Chapter 8, the analyses supporting these data are in Appendix C. The relationship between all variables, CA and within-domain MA equivalents are displayed in Figure 9.1 and Figure 9.2, respectively. When comparing between age-groups, the development of visuospatial and associative memory measures were not impaired, and within verbal memory only WM development was impaired across childhood. However, when comparing the entire age range across CA the development of visuospatial LTM, and verbal WM and LTM were impaired. In addition to this, across the MA-equivalent measures verbal WM development was impaired. These results indicate that trajectory analyses are more

sensitive to detect delay than age-group comparisons. This could be driven by floor effects, which were observed in visuospatial LTM, however, this was not present in verbal LTM, therefore the increased sensitivity of the trajectory analyses appears to be genuine. The finding that verbal LTM development was better than visuospatial LTM agrees with previous findings (Jarrold et al., 2007).

Discussing the uneven profile in terms of the trajectory analyses, the development of visuospatial LTM was impaired across CA, but not pattern construction raw scores. This measure did not correlate with CA, verbal score, or non-verbal scores. This indicates that in the DS group the development of visuospatial LTM was not reliant on the development of other within-format abilities. Spatial STM development was CA appropriate. Verbal and spatial WM abilities were not significantly different from TD abilities at the youngest CA in this study, but both developed significantly slower than the TD group. Verbal LTM abilities were significantly different at the lowest CA, but improved at a similar rate to the TD group. Spatial LTM abilities, although not delayed at the youngest CA, did not appear to improve at all across the CA included in this study. Digit span, in agreement with previous work, was impaired at onset and did not develop across CA, verbal fluency also did not develop, but was not impaired at the youngest CA assessed.

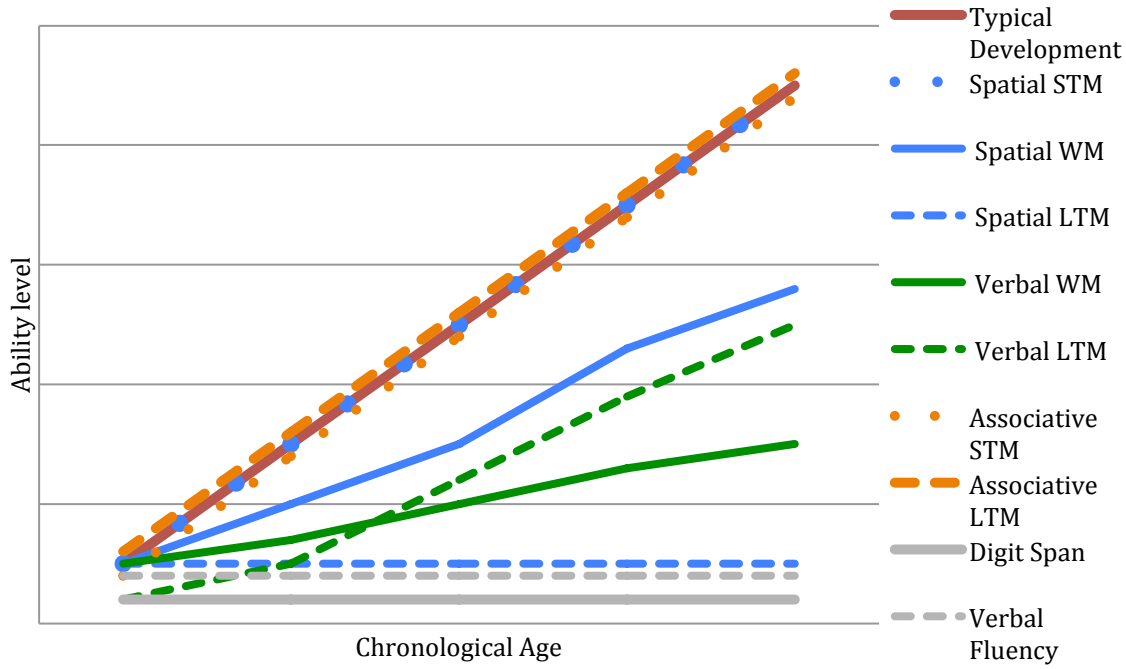

Figure 9.1 The relationship between dependent variable outcomes across the CA included in this study

A comparison of skills across within-domain MA equivalents, when only considering the overlapping sample is illustrated in Figure 9.2. Both spatial WM and LTM abilities were significantly impaired at the youngest MA, but improved faster than TD individuals matched on pattern construction abilities, resulting in higher scores in high-MA individuals with DS than TD participants. This means that participants with DS spatial memory abilities developed faster than their pattern construction skills, indicating that this is an area of uneven ability in the DS group, where the WM and LTM abilities have developed past the within-domain-expected ability levels for the TD population. Verbal WM skills were delayed at the lowest scores, and improved significantly slower than the TD group over verbal score. However, verbal LTM recall was MA-appropriate at onset, and also improved at a similar rate, as did verbal fluency. Digit span abilities were impaired at the lowest verbal score, but developed similarly across scores.

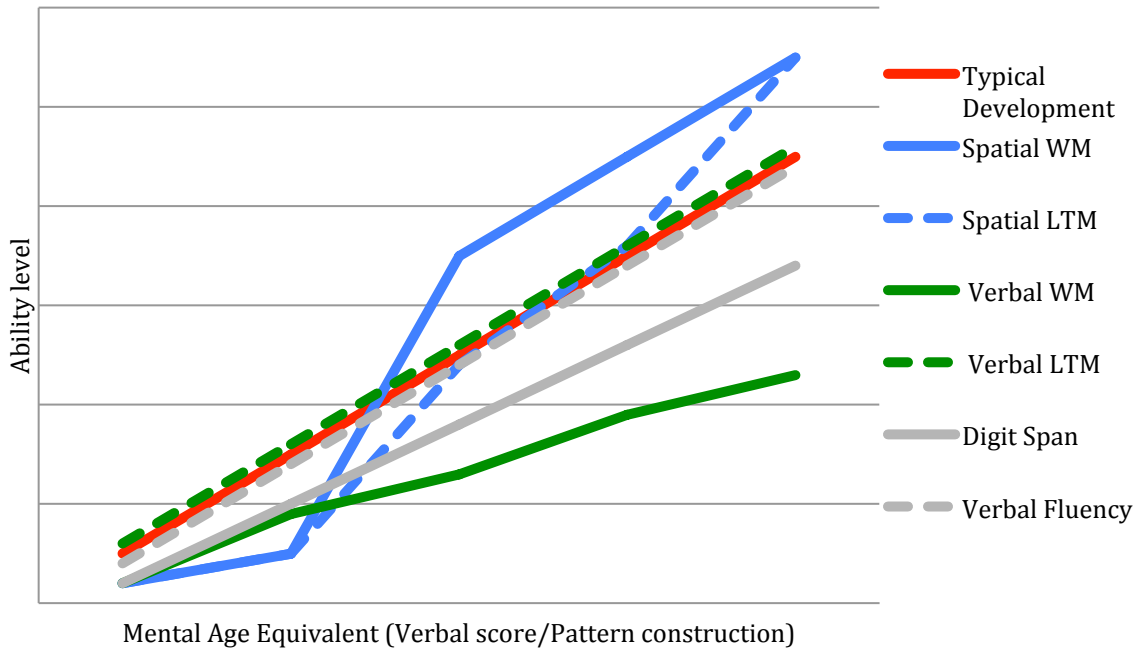

Figure 9.2 The relationship between dependent variable outcomes across within-domain cogntive measures included in this study

Alternatively, verbal WM development was impaired across CA and MA and correlated with CA, verbal score and pattern construction MA. Therefore, although this ability development was significantly impaired, it did appear to be associated with increasing CA, within-format MA and between-format MA measures.

The finding that verbal memory appears to be overall more impaired than visual memory development, could be explained by the greater loss of neural tissue in the left hemisphere than in the right, as the left hemisphere is associated with verbal functions (Jernigan et al., 1993). The literature also describes temporal limbic, but not parietal, microcephaly in the DS population, indicating the visual processing pathway may be more impaired than the spatial processing pathway (Goodale & Milner, 1992; Onorati et al., 2013). This uneven structural change could explain the dissociation seen between visuospatial LTM ability development, and visuospatial processing abilities. Perhaps the microcephalic alteration rewires the

brain to compensate in a manner that results in the disparate development of these abilities. Indeed, in the visuospatial assessments the only measure that did correlate with pattern construction measures was WM, and no measures correlated with CA, suggesting overall that this format of memory was developing in an atypical manner in relation to other cognitive abilities and across time. Visuospatial and visual specific abilities both utilise the amygdala, whereas spatial abilities are more reliant on the hippocampus (Kreiman et al., 2000). The findings of this thesis suggest that the typical synchrony between the development and the functionality of these structures may be impaired in the DS population.

Considering within-domain development of abilities in the DS group, all measures within verbal and associative memory had the same relationship to the TD group, whereas visuospatial measures had different relationships. This uneven development of visuospatial memory abilities was equal to a similar development of WM, but impaired LTM trajectory across CA.

Correlations of measures, whilst not indicating abilities are at the same level, do indicate similar rates of improvement. These are summarised in Table 9.1. In visuospatial memory the only correlation was between WM and pattern construction derived scores, indicating STM and LTM did not improve at the same rate as this ability. Furthermore, no measure correlated with CA or verbal score, suggesting the development of these are unrelated. These correlations, or lack of, in the visuospatial WM and LTM measures, were the opposite of the TD results, showing this is an area of cognitive developmental asynchrony that is unique to the DS group. The lack of correlation observed between visuospatial WM, LTM, and a measure of purely visual MA, supports the theory of unrelated development within this memory format, caused by altered neural structure.

Verbal LTM correlated with CA, verbal score, and pattern construction score; therefore although the development of visuospatial abilities may not relate to verbal outcomes, verbal memory ability development is related to development of visuospatial outcomes. The correlation with CA indicates that this ability improved with life experience and increased exposure to stimuli.

Associative STM did not correlate with CA, verbal or pattern construction abilities, whereas LTM did except for pattern construction. This shows that the development of associative LTM observed in the DS population was in synchrony with the development of other formats of cognitive development. This supports the integrative nature of associative memory function, and suggests that although STM may have ceased to develop, there is still potential to capitalise on between-format associative LTM abilities in the DS population.

Table 9.1 A summary of overall and developmental delay in age-group comparisons, delay over CA and MA in trajectory analyses, correlations between dependant variables and CA, verbal and non-verbal scores and other measures from experimental chapters.

Domain	Memory	Early and late childhood comparisons		Trajectory analyses		Correlations						Point of interest
		Impaired overall	Delayed development	Delayed development (CA)	Delayed development (MA)	CA	Verbal Score	Non-verbal raw	Adaptive behaviour	Visual WM MA	Verbal WM MA	
Visuospatial	STM	Y	N	N	-	N	N	N	-	-	-	Same as TD in late childhood
	WM	Y	N	N	N	N*	N*	Y	-	N*	-	
	LTM	Y	N	Y	N	N*	N*	N*	-	N*	-	

Verbal	WM	Y	Y	Y	Y	N*	N*	Y	-	-	Y	
	LTM	Y	N	Y	N	Y	N*	Y*	-	-	Y	
	Learning	Y	Y	-	-	N	N	N	-	-	N	
	Decay	Y	Y	-	-	Y	Y	Y	-	-	N*	
Associative	STM	Y	N	N	-	N	N	N	N	-	-	
	LTM	Y	N	N	-	Y*	Y*	N	N	-	-	Same as TD in late childhood
	Decay	Y	N	-	-	-	-	-	-	-	-	

* Correlation opposite to that seen in TD group, Y= significantly different at $p<0.05$ level, N= non-significantly different, - = analysis not carried out

9.5 Associations with mouse model literature or Alzheimer's risk

Some of the paradigms in this study were directly based on mouse models of DS. As discussed in Chapter 3, the findings of this study did not agree with the outcomes of the mouse literature, where object STM was impaired, but object-in-place STM was not (Hall et al., 2016). Object STM was not impaired in the mouse model, whereas overall abilities were impaired in human participants. However, these results supported our hypothesis based on human object memory results, meaning that the data from the mouse literature neither aligned with previous studies of human participants, nor was replicated here with a low control paradigm. This suggests that mouse models may not be as comparable to human results as had been hoped.

Mouse model studies are beneficial to increasing our understanding of outcomes as the control and rigour of the methods can be more extreme than is possible in the human population. Therefore, the failure of this study to replicate mouse model outcomes should not be interpreted as a failure of the mouse model literature, just the importance of caution when attempting to relate human and mouse model outcomes.

Although a major motivation of this thesis was to connect the work of infant and adult streams in the LonDownS consortium, it was not within the scope of this thesis to discuss the results in context of these other groups. Primarily this is because the other groups have not concluded their research, although also for the sake of brevity it was not desirable. Previous studies have found that impaired associative LTM was implicated in increased risk of AD and other dementias (Crutcher et al., 2009). This study showed that associative LTM was a strength in

the DS population, improving over time to be similar to the TD population in late childhood. This similarity in abilities suggests that this might be a sensitive measure for the onset of AD symptoms in both TD and DS populations.

9.6 Limitations and future work

The small N in the early childhood DS group sometimes limited comparisons between early and late childhood, as many participants were excluded in higher control tasks. Some of the eye-tracking tasks also had limitations, the object-in-place task failed to measure this ability as no age group or group performed significantly above chance in either trial. The object memory task failed to definitively measure memory due to the absence of a central stimulus prior to the test trial. By definitions used in this study, STM measures must not demand any manipulation or rehearsal of data, which prohibited any measure of verbal STM being derived from the BAS 2 assessments. Digit span could be an example of verbal STM as there is not an interval for rehearsal, however it cannot be certain that participants were not rehearsing or manipulating digit data. Eye-tracking is an ideal methodology to assess STM, as there are no instructions or explicit responses required, a verbal eye-tracking study would require reading or response to auditory stimuli. A good future study should include verbal STM along with WM and LTM assessments, to enable comparison of the trajectories of all three measures. In addition to this missing feature of this study, there was no associative WM measure. The associative memory measure was used as it had previously been validated with TD infants, showing it was appropriate for those with low MA. However, the same features that made this paradigm ideal for use in this population also prohibited the derivation of a WM measure. In future work it would be interesting to investigate

the synchrony in development of associative STM, WM and LTM, at higher levels of cognitive control.

A limitation of the TD sample was that the non-verbal MA scores calculated from picture recognition were significantly higher than the mean CA. This suggests that the sample were not entirely representative of the general population. In many ways, this is an inherent risk of sampling the TD population, specifically with children. Parents who sign their children up to take part in scientific research studies are more likely to be engaged in academia and their children's academic development. This increases the likelihood that the same children are exposed to a higher frequency and range of cognitive and behavioural stimulants and environments. Although it is preferable to have a sample that are representative of the population, these measures were used either in correlations within group, or as covariates in between group comparisons. This means the deviance from the norm in the sample should not affect the interpretation of dependant variable abilities and development in the DS group.

Another limitation of this thesis is the risk of multiple comparisons. Given that the samples in each analysis were related, and no correction for multiple testing was carried out, it is possible that some of the results were false positives. This is always a risk in carrying out a large multidisciplinary study and, although no predictions about effect sizes were made, a power calculation was carried out. With $\alpha=0.05$, and $\beta=0.2$, with the group N=43, N=32, this study had an 80% power to detect an effect size of 0.654, which is a large effect size. The majority of effect sizes observed in this study were small to medium, although large effect sizes were seen, notably the group differences in verbal WM and decay of verbal information from WM to LTM.

One of the major limitations of working with children with DS is the increased variability with task engagement within individuals over time, especially given our finding of impaired sustained attention (Wishart & Duffy, 1990). Although the maximum considerations were given to the needs and disposition of each individual child, it is always possible that some under performed in specific tasks due to individual differences that cannot be controlled for. Specifically, the harder the task, the more likely that the child would avoid engaging and perform below their actual ability level (Wishart, 1993). Although there was no obvious task where this behaviour was more noticeable than others, it is likely that the behaviour of each participant worsened over the testing session. For this reason it may be beneficial to randomise the order of testing more, although some tasks will always come later, for example, test of LTM. It is possible that this exaggerates the impairment observed in LTM abilities, and a good future study should control for this effect.

9.7 Implications and conclusions

The current study identified many novel findings. These results, and their implications are now discussed, addressing first visuospatial, then verbal, then associative memory.

Within visuospatial memory abilities, as the level of control increased, from STM to LTM, the developmental trajectory deviated farther from the TD trajectory. Therefore, the DS group appeared most typical in immediate, low control assessments, but as further cognitive demands were required ability levels decrease. This indicated that some feature of encoding or storage of visuospatial information might be impaired in the DS population. In STM, the early childhood group did not perform above chance until the second trial, indicating that the DS

group were capable of performing the task, but required longer exposure to the information for STM to function. However, this study was the first to show that the rate of forgetting of visuospatial data from WM to LTM assessments was not significantly different between DS and TD groups. Therefore, even though LTM is impaired developmentally, the implications are that if an item can be stored in WM, it is more likely to enter LTM. Visuospatial LTM abilities did not improve with CA, but did improve with processing raw scores, indicating that cognitive development is necessary for increased visuospatial LTM abilities. However, this could also be a feature of cross-sectional comparisons. Perhaps with visuospatial information, it is better to focus on short-term learning and processing, and to rely more on richer memory formats for long term memory and behavioural changes in the DS population.

Examining the mean N recalled in primacy, mid-list and recency reveals that in both groups, the items presented first were recalled best. This could be due to increased rehearsal time, or to limited capacity for visuospatial information. Items with a higher edge-ness rating were also better recalled, suggesting that overcrowded data were less well encoded than more unique spatial positions. The real-world implications of these findings are that visuospatially presented information should be in small groups, preferably with each item separated from the others.

Interestingly verbal LTM developed faster than WM across both CA and MA-equivalent measures in the DS population. By late childhood both DS and TD groups recalled around 100% of items recalled in the verbal WM measure. Therefore, focusing on verbal WM development has the potential not only to increase these abilities, but also to increase the performance of verbal LTM, if LTM capacity is not

already saturated at this point. The rates of learning over repeated WM trials was significantly impaired in the DS group, but the development of learning was not significantly different between groups. Increased exposure to information increased recall in the DS group, which is comparable to the object memory behaviour in early childhood. It would be interesting to see how many exposures are required for the ceiling of improvement to be reached at each age group. This finding would permit parents and teachers to have a target amount of exposures for verbal information to ensure WM (and thus LTM) encoding. The reason the ceiling N of exposures would be useful would be to prevent over-exposure, which could lead to fatigue or boredom when engaging in the tasks. The rate of decay of verbal information was also different in DS and TD population, although the development of change in this ability was again similar, indicating another area where the development of DS cognitive abilities was not as atypical as could be expected.

In verbal WM only recency developed at a comparable rate to TD, but in LTM recency and primacy developed comparably. Therefore, in verbal memory assessments there was a typical development of recall of later list items, whereas in visuospatial memory the development of recall of early list items was more typical. This suggests different mechanisms in encoding methods of verbal and visuospatial data within the DS population. A preference for late list items could be due to reduced requirement of rehearsal, or related to the preferential encoding of edge items, which was present in both assessments. Overall, these findings suggest that teachers should avoid presenting information in large groups, and particularly in verbal memory, should ensure WM encoding, as verbal memory appears to lose less information between WM and LTM storage modes.

Associative STM and LTM abilities were impaired, but developmental rates were similar to TD at the low-level assessed in this study. STM did not significantly improve with CA, but LTM abilities did still improve across CA. LTM abilities also correlated with verbal and non-verbal measures. None of the LTM associations were seen in the TD group, indicating that associative LTM continues developing later in the DS population than in TD individuals. In this measure the DS group did not perform above chance except for in the delayed trial in late childhood, indicating this ability is either not functioning until this age, or that this measure could not capture this behaviour until this age-group. The implications of the relatively typical nature of the development of these abilities, is that whilst within-domain associative recall development is impaired, between-domain associative memory is a relative strength of this population (Visu-Petra et al., 2007). Data recall could be improved by binding multiple formats of memory, increasing the likelihood of the information being recalled at a later time.

The development of sustained attention and cognitive flexibility were impaired in the DS population, but neither the overall performance nor the development of inhibition or cognitive top-down control was impaired. Risk of SRBD significantly impaired sustained attention in the TD group, but had no effect on any measure in the DS group. This could be due to an asynchrony of these features in DS development, or a genuine finding that sleep does not impaired cognitive function. Further studies are required to ensure this was not an error caused by cross-sectional sampling.

Overall, although verbal memory development was impaired compared to visuospatial STM and WM, visuospatial LTM development was most impaired across CA in the DS group. However, visuospatial WM and LTM and verbal LTM

abilities improved at within-domain appropriate rates, only verbal WM development was impaired across development. These findings not only illustrate the disparity between CA and cognitive development in the DS population, but also the uneven cognitive development of memory abilities across childhood. Another interesting result that was shown in Table 8.3, was the difference between variance explained by verbal and non-verbal scores. In the DS sample, pattern construction derived measures explained significant variance of verbal memory measures, spatial WM and verbal fluency. However, the verbal MA equivalent only explained significant variance in verbal fluency and associative LTM abilities. These results suggest that visuospatial abilities are associated with more cognitive outcome measures than verbal abilities. The implications of this are that emphasis on improving non-verbal abilities may have better cognitive outcomes on memory development than focusing on improving verbal abilities. The synchrony of the development of abilities in the verbal memory assessments indicates this was an area of relatively even cognitive development within the DS population. In addition to this, these correlations were the most comparable with those seen in TD individuals, supporting the relatively typical relationship existing within the development of this memory format. However, rates of learning and forgetting of verbal data were impaired in the DS group, whereas rates of forgetting of visuospatial data was not impaired, supporting the evidence of relative strength of visuospatial compared to verbal abilities overall.

In reality, the majority of results described in this study were novel findings. This is not because the study itself was exceptionally innovative, but because the focus of research for too long has been comparisons on either one or multiple cognitive measures, between two groups matched on another measure. The

characterisation of delayed and appropriate behaviours in the DS population in childhood and upwards has been almost exhausted. The future of this research should focus more on development, specifically the relationship between the development of different within- and between-format abilities. A greater understanding of the connectivity of development would permit more personalised interventions to maximise the improvement of outcomes. For example, if it is found that an early ability in verbal tasks improves later life outcomes in five memory abilities, whereas good visual processing skills improves later life outcomes in only three, then verbal skills can be made the focus of interventions. New tasks need to be designed that enable assessment of memory abilities in atypical populations without floor affects, and that can be adapted and used to assess development at multiple time points without the individual being over-familiarised with the stimuli. Future studies should also aim to examine the development of these abilities not only across development, but also across syndromes. Although a detailed picture of the cognitive development of a syndrome is informative, comparing between two atypical groups has the benefit of highlighting differences that are syndrome-specific, rather than due to overall intellectual disability. Future research that focuses on longitudinal, cross-section, cross-syndrome memory development, has the potential to reveal far more than the simple case-control group comparisons of the past.

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Chapter 10 Appendix A: Demographic Forms

Demographic forms

BIRKBECK CENTRE FOR BRAIN AND COGNITIVE DEVELOPMENT

University of London, 32 Torrington Square, London, WC1E 7JL

We should be grateful if you would kindly complete the following questions in order to give us some background information about you and your child. Some of these questions may not be relevant to the age of your child – please leave blank.

Parent(s) name .....

Address..... ..... Tel. No. .....

Mother's occupation .....

Father's occupation .....

Mother's level of education .....

Father's level of education .....

Most convenient time to be telephoned .....

APPENDIX A

Child's first name(s)..... Date of birth.....

Premature? YES/NO ..... (weeks) Birth weight ..... Present weight.....

Was the birth easy?.....

Did you take any medication during labour? .....

Was your child hospitalized at any time since birth? .....

Was your child breastfed? YES/NO If YES, for how long? .....

Has your child had any feeding problems? .....

Does your child have any brothers or sisters or a twin? YES/NO

If YES, please detail (names, birth order) .....

Has your child used a dummy? YES/NO

When did your child first sit on his/her own? .....

First crawl? .....

First stand? .....

Please describe your child's sleeping patterns .....

APPENDIX A

What time of day is your child most alert? .....

All children have strengths and weaknesses:

(a) have you noticed particular strengths in your child?

.....

.....

(b) have you noticed any particular problem areas (e.g. hearing/vision/behaviour)?

.....

.....

If your child has any visual problems, does s/he wear glasses or has he/she had any corrective treatment? .....

Does your child wear a hearing aid? .....

Has your child ever suffered a head injury, or had an incident and lost consciousness (note if greater than 5 mins)? .....

Is your child taking any medication? .....

Please describe your child's response to strangers .....

Are there any pastimes your child particularly enjoys? .....

Please describe your child's beginnings of language?

does he/she understand any words? How many? .....

does he/she produce any words or sounds? How many? .....

APPENDIX A

Does your child have a favourite toy? .....

Does your child watch television? YES/NO

If YES, please describe (average no. of hours per week, type of programme)

.....

Have you and your child participated in any other research studies and, if so, which one(s)?.....

Would you like to take part in our studies? YES/NO

If YES, is there any particular time of day or day of the week that would be most convenient for testing? .....

Thank you for your time and co-operation in filling out this questionnaire. All information that you provide will be treated as strictly confidential. (If completing at home, please return in FREEPOST envelope or take bring you on the day of your appointment).

SIGNED .....

DATE .....

APPENDIX A

Early pre and postnatal history form

Research staff	
Respondent	
Date	
Baby's name/ID	
Baby's DOB	
Baby's gender	

APPENDIX A

Ethnic Origin

☐ Asian or Asian British-Indian	☐ White-Irish
☐ Asian or Asian British-Pakistani	☐ Other White background
☐ Asian or Asian British-Bagladeshi	☐ Mixed White and Black African
☐ Chinese	☐ Mixed White and Black Caribbean
☐ Other Asian background	☐ Mixed White and Asian
☐ Black or Black British-African	☐ Other Mixed background
☐ Black or Black British-Caribbean	☐ Other Ethnic background
☐ Other Black Background	☐ Do not wish to answer
☐ White-British	

Please tick the box which most closely describes your child, or if you do not think your ethnicity is listed, please fill in your own description below:

Birth Information

Age when grandmother conceived mother			
Age when mother conceived infant			
Birth	Vaginal ☐	Cesarean ☐	
Premature	Yes ☐	No ☐	
Birth measure	Weight:	Height:	NK* ☐
Current measure	Weight:	Height:	NK* ☐
Father current	Weight:	Height:	NK* ☐
Mother current	Weight:	Height:	NK* ☐
Current measure (heart rate/blood pressure)	HR:	BP:	
Poor weight gain	Yes ☐	No ☐	NK ☐
Eye colour			

* NK: Not known

Apgar Score (total 0-10)

Appearance	
Pulse	

APPENDIX A

Grimace	
Activity	
Respiration	

Temperament

Temperament	Easy☐	Difficult☐	Passive☐	NK☐
Stubbornness	Easy☐	Difficult☐	Passive☐	NK☐
Difficult to soothe (colic)	Yes☐	No☐	NK☐	
Strategies used to calm				
Sucking reflex	Good☐		Bad☐	

At Home

Type of play	Joint☐	Individual☐	Both ☐	Other☐	NK☐
Did your child attend nursery?	Yes☐		No☐		NA☐
Did your child have a child minder?	Yes☐		No☐		NA☐
TV Exposure	Little☐		Moderate☐		Lots ☐
Exposure to touchscreen devices	Little☐		Moderate☐		Lots ☐
Exposure to the outdoors	Little☐		Moderate☐		Lots ☐
Does your child hear more than one language at home?	Yes☐ Specify:		No☐		
Physical exercise level	High ☐ (>1hr/day intense)		Medium☐ (15mins/day intense)		Low ☐ (10mins/day intense or less)
Eye contact	Normal☐		Difficult to engage☐		NK☐
Sleep pattern	Regular☐		Irregular☐		NK☐
Feeding	Bottle☐ Formula☐ Breast☐ Length: Further information:				

APPENDIX A

Developmental History

					Age if known:
Gross motor	Early☐	Average☐	Late☐	NK☐	
Fine motor	Early☐	Average☐	Late☐	NK☐	
Social	Early☐	Average☐	Late☐	NK☐	
Self-help	Early☐	Average☐	Late☐	NK☐	
Smile	Early☐	Average☐	Late☐	NK☐	
Babble	Early☐	Average☐	Late☐	NK☐	
Say first word	Early☐	Average☐	Late☐	NK☐	
Sit	Early☐	Average☐	Late☐	NK☐	
Stand	Early☐	Average☐	Late☐	NK☐	
Crawl	Early☐	Average☐	Late☐	NK☐	
Walk	Early☐	Average☐	Late☐	NK☐	
Climbed stairs	Early☐	Average☐	Late☐	NK☐	
Developmental regression	Yes ☐	No ☐		NK☐	

Family and Household

Household income (optional)	
Family size (immediate)	

	Siblings & Parents:					
	Mother	Father	Brother/Sister 1	Brother/Sister 2	Brother/Sister 3	Brother/Sister 4
Relationship (full/ half)						
Gender						
DOB						
Received special education (Yes/ No)						
Difficulty with learning and/or maths (yes/no)						
Speech/language delay and/or impairment (yes/no)						
Premature birth (yes/no)						
Highest level of education						
Occupation						

APPENDIX A

During Pregnancy

We understand that the following questions are not specifically related to the cause of DS, but we are just trying to see if they play a role in individual differences in children.

Did the mother:	
Take folic acid supplements	
Smoke	
Drink alcohol	
Exercise	
Know their baby had DS	
Take psychoactive medication:	
i) CNS depressants	
ii) Opiates	
iii) Antipsychotics	
iv) Hallucinogens	
v) Other	
Take any other medication during pregnancy (if so, please specify)	
Did your child move a lot during pregnancy?	

General Questions

What 3 things do you find most difficult in your child?	1)
	2)
	3)
What are the 3 things you most like?	1)
	2)
	3)
What things does your child like?	1)
	2)
	3)
What things does your child **not** like?	1)
	2)
	3)

APPENDIX A

Therapy

Has your child received any therapy (speech/language)? If so, when did they start and what is the frequency of therapy?	1)
	2)
	3)

Nutrition

Please give some information about your child's nutrition below:

Comments

Please leave any comments you wish to make, or any other further information you believe to be relevant, below:

APPENDIX A

Medical History Form:

Research Staff	Baby's Name/ID
Date	Baby's DOB
Respondent	Baby's Gender

	Baby		Biological Mother		Biological Father		Siblings, aunties, uncles, grandparents etc	
	Y/N	Age of Onset	Y/N	Age of Onset	Y/N	Age of Onset	Y/N (if yes, maternally or paternally derived)	Age of Onset

Down's Syndrome

Trisomy 21								
Nondysjunction (origin)								
Mosaic								
Paternally/ Maternally derived								
Any other comments								

Neurodevelopmental Disorders

Speech/ Language Delay								
Developmental Delay								
Learning Disability								
Tubercular Sclerosis								
Fragile X								
Autism Spectrum Disorder								
Alzheimer's Disease								
Neuromuscular Disorder								
Cerebral Palsy								
Motor Defect (other)								

Known Genetic Disorder type								
Other (specify)								

Sensory

Vision Impairments								
a) Vision Corrected								
Wearing Spectacles								
Strabimus								

Sensory

Hearing Impairments								
a) Hearing Corrected (hearing aid, other)								
Recurrent Ear Infections								
Pressure Equaliser Tubes								
Glue Ear								
Other								

Mental Health

Bipolar Disorder (manic/ depressive)								
Depression								
Anxiety Disorder								
OCD								
Schizophrenia								
Personality Disorder								
Self-Injuring Behaviours								
Suicide Attempt								
Psychiatric Disorder								

ADHD								
Eating Disorder								
Sleep Disorder								
a) Insomnia								
b) Narcolepsy								
c) Frequent waking								
d) other								
Victim of abuse								
Substance abuse (type)								
Other								

Allergies

Food								
Skin								
Eczema								
Psoriasis								

Allergies

Psoriasis								
a) Psoriasis medication								
Environmental								
Medication								
Other								

Head/Brain

Microcephaly								
Macrocephaly								
Head circumference								
Structural Abnormalities								
Inflammation								
Gaps in Blood-Brain barrier								
Meningitis								
Encephalitis								
Febrile Seizures								
Seizure Disorder								
Epilepsy								
Have you had an EEG before								

If yes, results (normal/abnormal)								
Have you had an image of your brain before								
If yes, type								
a) CT								
b) MRI								
c) PET								
Results (normal/ abnormal)								
Other comments								

Pulmonary/Cardiovascular

Congenital Heart Defect								
a) surgery								
Atrioventricular septal defect in baby								

Pulmonary/Cardiovascular

Abnormal breathing								
Asthma								
Lung Malformations								
Frequent pneumonia								
Aspiration								
Other Cardiac Malformation								
Cyanosis								
Other								

Endocrine/Metabolic

Thyroid Disease								
Hypothyroidism								
Hyperthyroidism								

Diabetes								
Asthma								
Hyper/ hypoglycaemia								
Pancreatic Insufficiency								
Growth Disorder								
Obesity								
Cholesterol Levels Abnormality								
Other comments								

Immunologic

Autoimmunity								
Coeliac Disease								
Sickle Cell Anaemia								
Recurrent Infections								
Sepsis								
Immune Deficiency								
Jaundice								
Vaccinations (list):								

Immunologic

Other comments								
Colds								
a) length of cold (last a long time)								
b) do they lead to infections?								

Cancer

Type								
1. Leukemia								

a) Blood count								
Other information								
2. Prostate cancer								
Other information								
Other type (specify)								

Other Conditions

Stenosis
Specify
a) details

Current Medications/supplements

Type
Dose

Current Medications/supplements etc

Reason
Supplements
Coffee of cups (per day)

Gastrointestinal

Dysphagia
Reflux
Feeding difficulties
Hirshburg's

disease (HD)								
Hernia								
Gastrointestinal Disorder								
Other comments								

Urinary/Bowel

Renal Malformation								
Discoloured urine								
Irritable Bowel Syndrome								
Other Comments								

Mouth/Teeth

Cleft lip								
Cleft palate								
Speech Difficulties								
Neonatal Teeth								
Dental abnormalities								
Other comments								

Neck/back, Orthopaedic, skin or any other conditions

Spinal Abnormalities								
Fractures								
Joint Dislocation								
Birth marks								
Eczema								
Skin Infection/ Abcesses								
Pigmentation								
Other comments								

Chapter 11 Appendix B: Task order

Brief overview of tasks administered but not analysed herein

Task Order	Day 1 or 2 of DS assessment	Procedure	Maximum time taken for assessment (minutes)
Grammar and Phonology Scale	1	Standardised assessments	10
Tower of London	1	Standardised assessments	15
Finger-Nose test	1	Standardised assessments	1
NEPSY tracks	1	Standardised assessments	10
BREAK			
Memory of Context	2	Eye-tracking	3
Go/No-Go	2	Computer task	5
Old/New effect	2	EEG	5
Mismatch negativity	2	EEG	5
Social/non-social resting EEG	2	EEG	2

Memory of Context

This is a measure of context memory. Six study trials showing two copies of an image 8° x 8° on a background 12° x 20° were displayed. Two conditions are displayed alternatingly, for example, two images of a cat on a stripy background, followed by two images of a pig on a wavy background, see Figure 3. Each study

trial was presented for 8 seconds. Four study trials ran without central stimuli; meaning each pair of images is seen four times. The test trials involved presenting one familiar image on both familiarised backgrounds; one background will be familiar for the image and one will be novel. The test trial was presented for 8 seconds, and the whole procedure lasted 1 minute. The outcome of this test is looking time to the unfamiliar image/context relationship, as an indication of context memory.

Go/No-Go

This is a measure of inhibition and attention (Eagle, Bari, & Robbins, 2008). This is a computer task where the participant was seated in front of a laptop and instructed "Circles are going to appear in the middle of the screen, as soon as you see a circle, press the space bar. If the circle is red, don't press the space bar". This was then followed by a short practice session. The participants were reminded "don't press for red". This was followed by the full Go/No-go consisting of 70 trials with 15 red circles (No-go trials). Circles were presented in the middle of the screen, correctly pressing the button for a non-red circle resulted in a */click/,* sound, incorrectly pressing the button for a red circle resulted in an */uhoh/* sound. The outcome of this test is average reaction time, number of inhibition errors (pressing for red) number of omission errors (not pressing for non-red). This took approximately 5 minutes. Inclusion in this task relied upon adequate cognitive abilities to understand the instructions, attention to stay on task for an extended period of time and motor abilities to press the button. Many of the younger or more cognitively impaired participants with DS were unable to attempt this task.

APPENDIX B

Old/New effect

This is an EEG task measuring memory (Curran, 1999; Wilding, 2000). The individual was instructed, “I’m going to show you some pictures, I want you to try and remember them” and 13 images of toys were presented. Each image was on screen for 700 milliseconds with a 300 milliseconds interval where a central stimulus was shown. This was repeated twice. The participants were then instructed, “I’m going to show you some more images now, you don’t have to try and remember them”. They were then presented with novel images interspersed with the familiarised images. Each image was onscreen for 700 milliseconds with a 300 milliseconds interval where a central stimulus was shown. The 13 familiar images were shown, as were 27 unfamiliar images, making a total of 40 images shown. This lasted 3 minutes. The brain activity in familiar vs. novel images was compared to make inferences about the mechanisms involved in memory.

Mismatch negativity (MMN)

This is an ERP task measuring the subconscious processing of mismatches in the environment (Mahmoudian et al., 2013; Naismith et al., 2012; Petermann et al., 2009). This version of the task involved a series of sounds being presented, 70% of which are the standard, 15% are a speech mismatch, and 15% are a pitch mismatch. The experimental stimuli were three acoustically-matched vowel sounds, namely, the standard, the speech deviant, and the pitch deviant. The standard was an /u/ sound with a frequency of 500 Hz. The speech deviant was an /i/ sound with a frequency of 500 Hz. The pitch deviant was an /u/ sound with a frequency of 650 Hz. The intensity of the sounds was 70 dB SPL. The duration of each sound was 100 milliseconds and they were presented every 700 milliseconds. The aim was to

present at least 200 stimuli as a minimum, and 600 as a maximum. To keep the participants entertained during the process, a silent cartoon was played silently to maximise the quality of the data. This lasted 5 minutes. The same visual stimuli were presented to all participants to control for any effect of visual input.

Resting (social/non-social)

This is an EEG task measuring resting brain activity when presented with social or non-social stimuli. This has two conditions that are counterbalanced across participants; the non-social condition was a 1-minute video of toys moving. The social condition was a 1-minute video of a person talking anecdotally, moving their hands in a manner to mimic the movements made by the toys in the non-social condition. This is to control for effects of visual motion on the neural signal. The outcome measure of this is the resting state brain activity in social vs. non-social conditions

Chapter 12 Appendix C: Further trajectory analyses of non-significant relationships

Between group comparisons of two developmental trajectories

In this section, trajectories of abilities are compared between DS and TD groups over CA. if an appropriate MA measure is available then the trajectories will also be compared across this measure, both between the whole groups, and a restricted comparison of only those with overlapping scores on the MA equivalent measure.

Visuospatial memory

Object memory

The goodness of fit of this model was only moderate (R^2=0.159), and the model explained a significant proportion of variance observed, $F(3,56)=3.54$, p=0.020, η_p^2=0.159. There was not a significant main effect of group on this outcome, thus the performance at youngest CA assessed was not significantly different between groups, $F(1,56)=1.93$, p=0.170, η_p^2=0.033. With the groups combined, CA significantly predicted performance on this task, $F(1,56)=4.97$, p=0.030, η_p^2=0.082. There was no significant interaction between CA and performance between groups, $F(1,56)=0.04$, p=0.850, η_p^2=0.001. As the interaction was non-significant then it can be concluded the CA had a significant main effect across groups, but that the groups did not develop at significantly different rates, as shown in Figure 12.1.

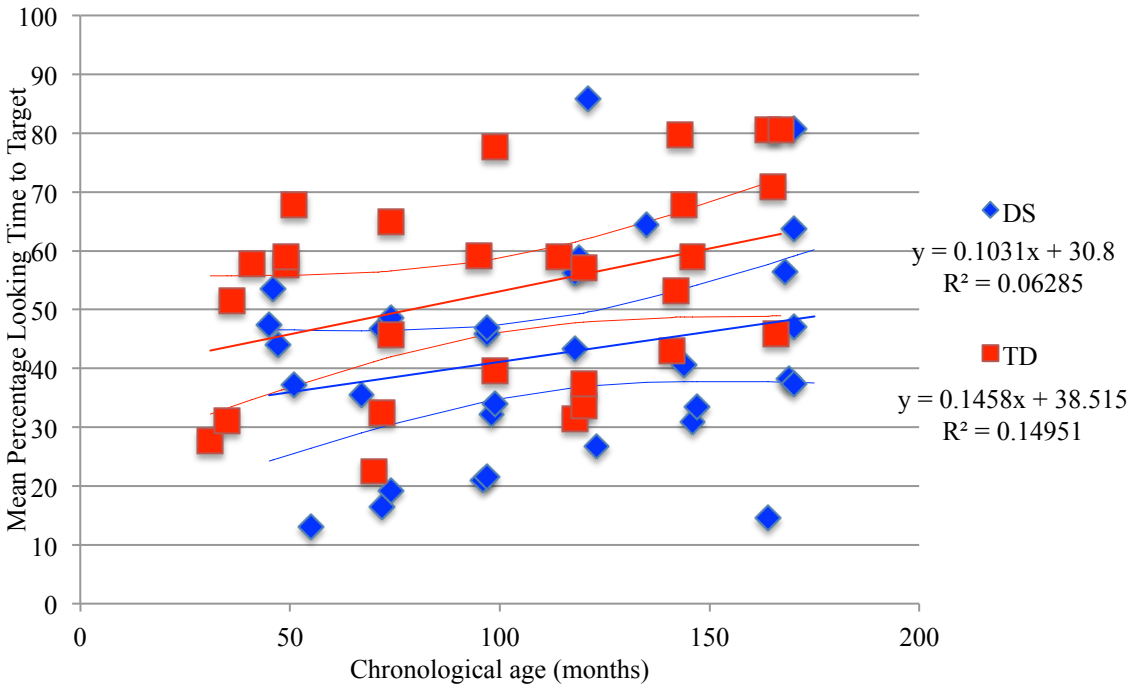

Figure 12.1 Mean percentage looking time to target in object memory task over CA in DS and TD groups, CI represent 95%

Object-in-place memory

The goodness of fit of this model was low (R^2=0.039) and the model did not explain a significant proportion of the variance observed, $F(3,56)=0.74$, $p=0.535$, $\eta_p^2=0.038$. The performance at youngest CA assessed was not significantly different between groups, $F(1,56)=0.91$, $p=0.344$, $\eta_p^2=0.016$. With the groups combined, CA did not significantly predict performance on this task, $F(1,56)=0.98$, $p=0.326$, $\eta_p^2=0.017$. There was not a significant difference in development of abilities measured by this task between groups, $F(1,56)=1.19$, $p=0.281$, $\eta_p^2=0.021$, as seen in Figure 12.2.

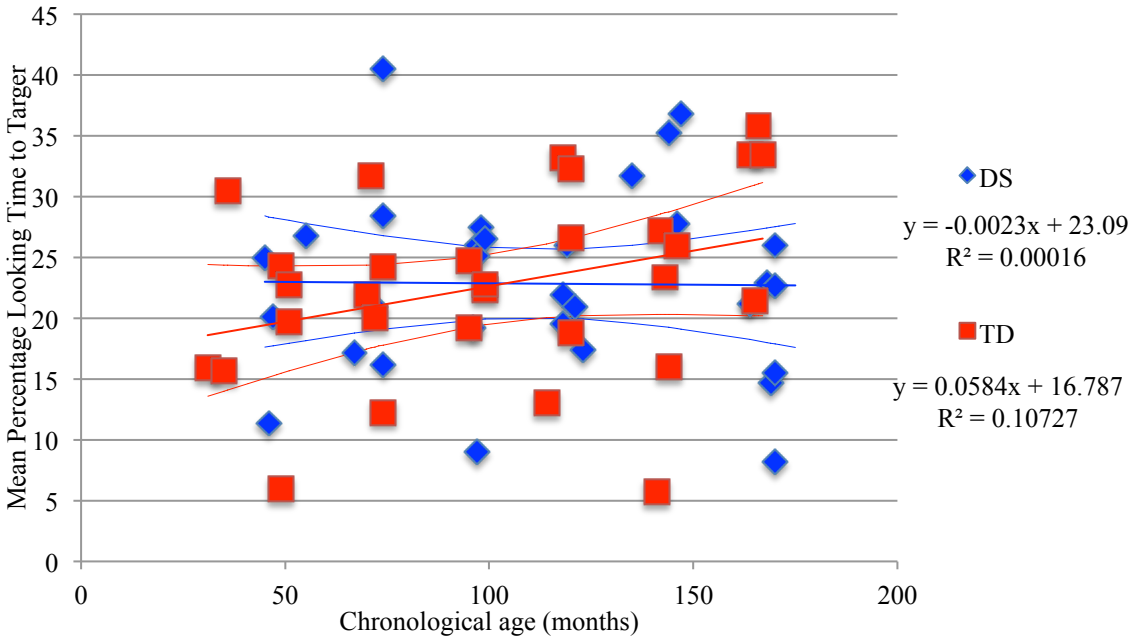

Figure 12.2 Mean percentage looking time to target in object-in-place memory task over CA in DS and TD groups, CI represent 95%

However, analysis of this task in Chapter 3 showed the performances of both groups was not significantly different from chance; therefore the data yield no strong interpretation. Given that no significant improvement is seen in the TD group with increasing CA, the main conclusion is that the task failed to assess abilities within the test population, rather than that neither group developed the required cognitive skills, see 3.3.3 Object-in-place memory.

Immediate spatial memory

The goodness of fit of this model was large (R^2= 0.468) and the model explained a significant proportion of the variance observed, $F(3,56)=16.93$, $p<0.001$, $\eta_p^2=0.468$. The performance at youngest CA assessed was not significantly different between groups, $F(1,56)=1.38$, $p=0.246$, $\eta_p^2=0.024$. With the groups combined, performance significantly improved with age, $F(1,56)=12.94$, $p<0.001$,

η_p^2=0.188. The rate of improvement was not significantly modulated by group, $F(1,56)=3.30$, p=0.074, η_p^2=0.056. While there was a weak trend for slower development in the DS group, the DS group improved at a third of the rate of the TD group (DS: 0.034, TD: 0.1), this is less readily interpreted as several individuals showed performance at floor levels. Performance at older ages suggests that, with greater sensitivity, the group comparison might resolve to performance at a lower level in the DS group at start, but developing at a similar rate, as shown in Figure 12.3. This is a commonly occurring issue in standardised testing with atypical populations and will in forthcoming analyses be highlight as 'floor-interference effect'.

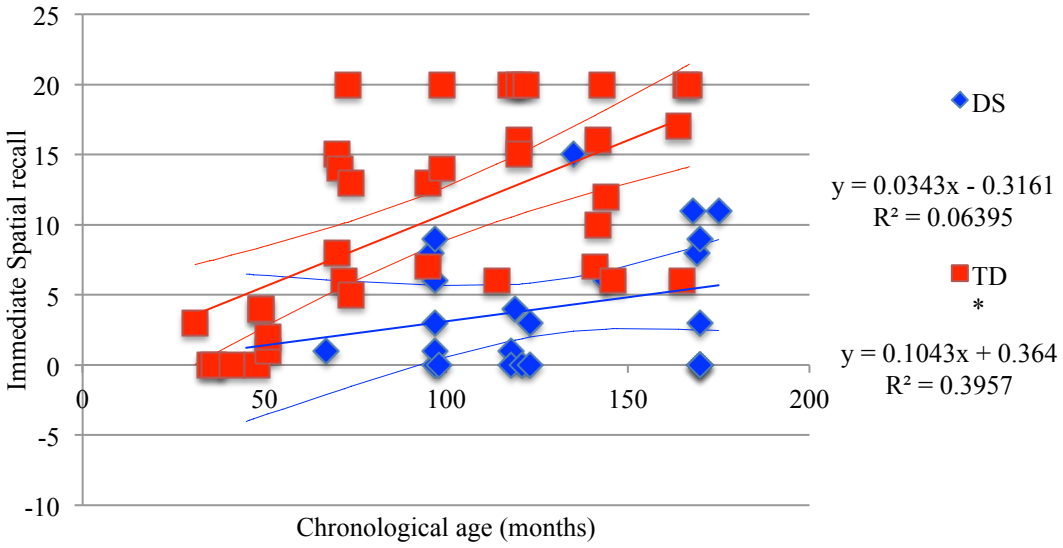

Figure 12.3 Immediate spatial recall in immediate spatial memory task over CA in DS and TD groups, CI represent 95%

Delayed spatial memory

The goodness of fit of this model is large (R^2=0.556), and the model predicted a significant proportion of the variance observed, $F(3,56)=23.38$, $p<0.001$, $\eta_p^2=0.556$. The performance at youngest CA assessed was not significantly different between groups, $F(1,56)=0.80$, $p=0.375$, $\eta_p^2=0.014$. With the groups combined, CA significantly modulated performance on this task $F(1,56)=6.20$, $p=0.016$, $\eta_p^2=0.100$. There was also a significant interaction between CA and group, $F(1,56)=8.51$, $p=0.005$, $\eta_p^2=0.132$. The DS group did not improve on this task (-0.007) whereas the TD group did slightly improve with CA (0.094). The performance disparity at onset was 3 points, as shown in Figure 12.4. Again, the interpretation of these results is limited by the high occurrence of floor results in the DS group, the floor-interference affect, which could conceal a relationship that would be apparent if performance below floor could be assessed.

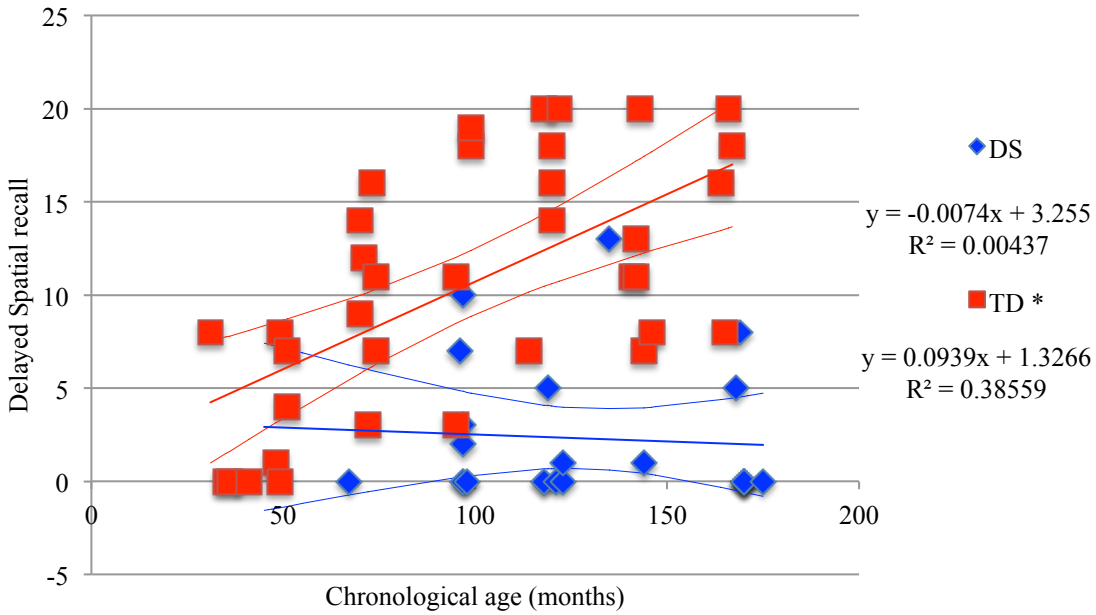

Figure 12.4 Delayed spatial recall over CA in DS and TD groups, CI represents 95%

APPENDIX C

Verbal memory

Immediate verbal memory

The goodness of fit of this model was considerable (R^2=0.724), and the model explained a significant proportion of variance observed, $F(3,63)=55.14$, $p<0.001$, $\eta_p^2=0.724$. The performance at youngest CA assessed was not significantly different between groups, $F(1,63)=2.75$, $p=0.102$, $\eta_p^2=0.042$. As only two participants were at floor on the immediate verbal memory task, the convergence of trajectories at early ages appears a robust result. With the groups combined CA significantly affected performance on this task $F(1,63)=59.62$, $p<0.001$, $\eta_p^2=0.486$. However, from similar early performance, the TD group improved more quickly with age, $F(1,63)=21.00$, $p<0.001$, $\eta_p^2=0.250$, with the DS group improving at a quarter of the rate of the TD group (DS=0.067, TD: 0.263), as shown in Figure 12.5.

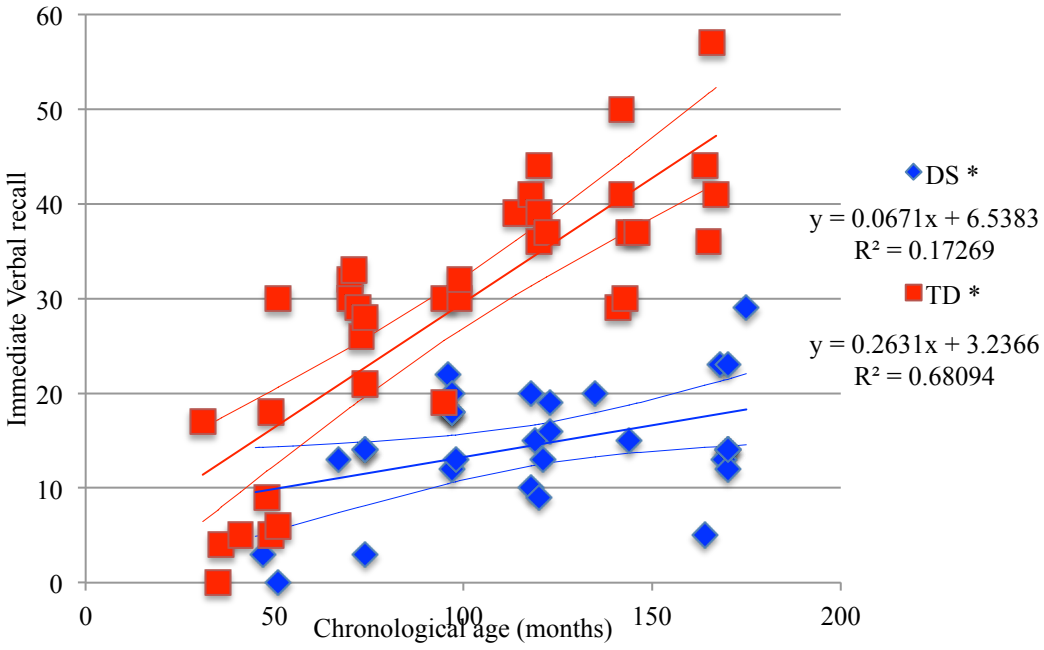

Figure 12.5 Immediate verbal recall over CA in DS and TD groups, CI represents 95%

APPENDIX C

Examining performance over verbal score and using only TD participants who fall within the same range of verbal MA distributions as the DS group, the results are as follows. The goodness of fit of the model was lower than in the CA or overall MA model, but still high (R^2=0.468). The two groups improved at significantly different rates over verbal score development, $F(1,38)=7.25$, $p=0.011$, $\eta_p^2=0.160$. The main effects of group, $F(1,38)=6.42$, $p=0.016$, $\eta_p^2=0.144$, and MA, $F(1,38)=16.64$, $p<0.001$, $\eta_p^2=0.305$, were also significant. Further analysis showed the DS group improved at less than half the rate of the TD group, with a performance disparity at onset of 7 points, as shown in Figure 12.6.

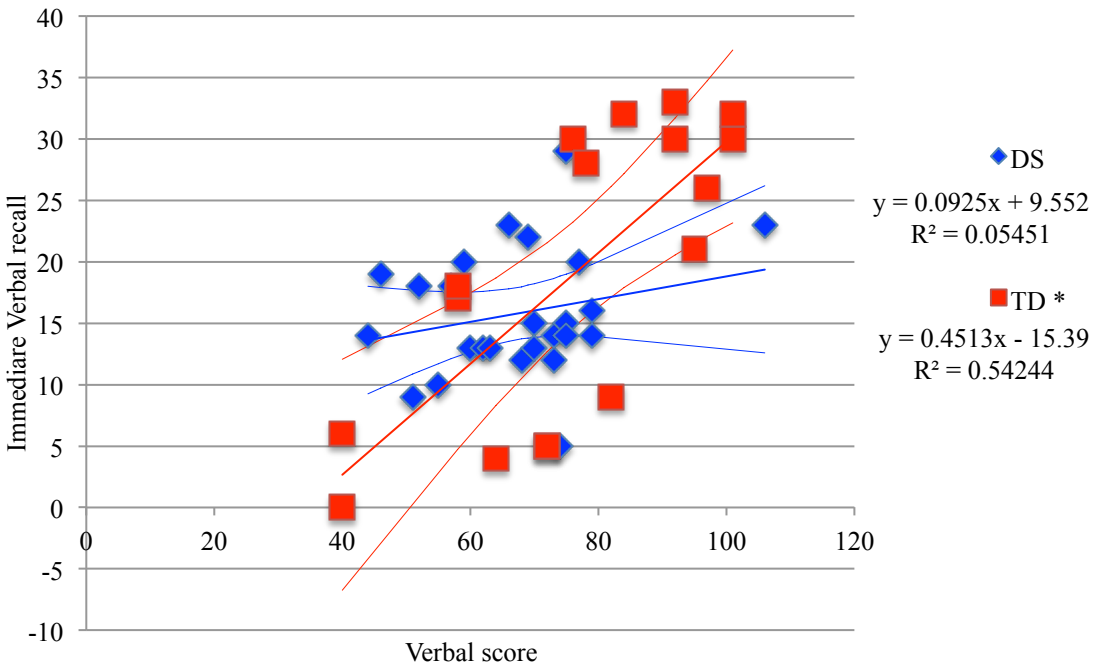

Figure 12.6 Immediate verbal recall over verbal score in DS and TD groups, CI represent 95%

APPENDIX C

Delayed verbal memory

The goodness of fit of this model was considerable (R^2=0.682) and explained a significant amount of the variance observed in this task, $F(3,63)=45.06$, $p<0.001$, $\eta_p^2=0.682$. The performance at youngest CA assessed was significantly different between groups, $F(1,63)=6.76$, $p=0.012$, $\eta_p^2=0.097$. With the groups combined, CA significantly modulated performance on this task $F(1,63)=58.43$, $p<0.001$, $\eta_p^2=0.481$. However, these main effects must be interpreted with caution as there was a significant interaction between CA and performance between groups $F(1,63)=8.83$, $p=0.004$, $\eta_p^2=0.122$. The DS group improved at half the rate of the TD group (DS: 0.048, TD: 0.108). The performance disparity at onset of 4 points, as shown in Figure 12.7.

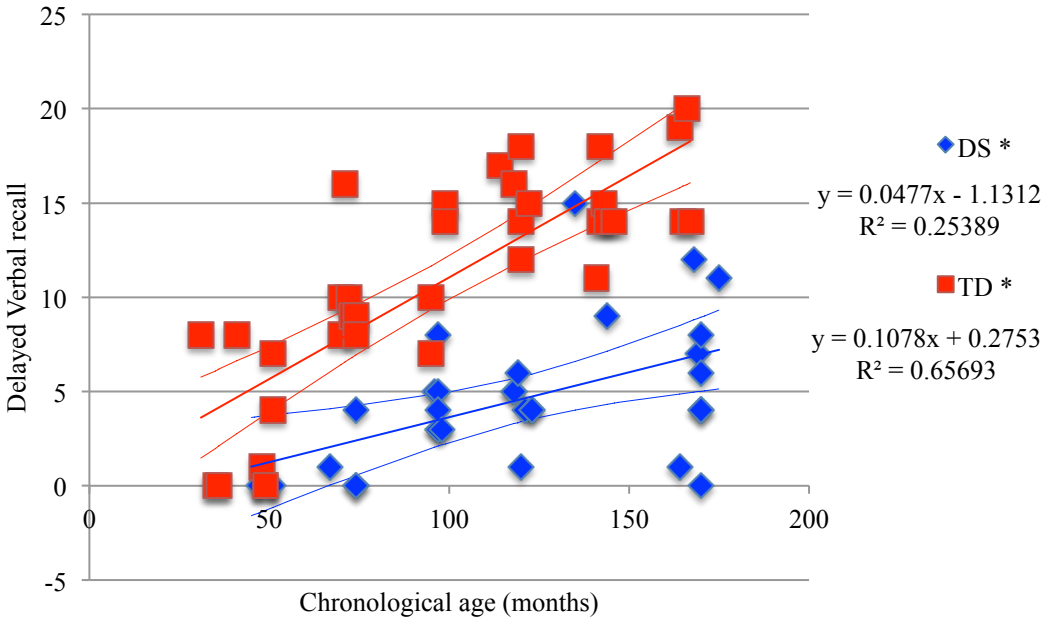

Figure 12.7 Delayed verbal recall over CA in DS and TD groups, CI represents 95%

APPENDIX C

Examining performance over verbal score and using only TD participants who fall within the same range of distributions as the DS group the results are as follows. The goodness of fit of the model was lower than in the CA or overall MA model (R^2=0.393). The two groups delayed verbal recall abilities developed at similar rates over verbal score development, $F(1,38)=1.89$, $p=0.177$, $\eta_p^2=0.047$. Delayed verbal abilities at onset were not significantly different between groups, $F(1,38)=1.62$, $p=0.212$, $\eta_p^2=0.041$. Across both groups verbal score significantly modulated delayed verbal recall, $F(1,38)=11.98$, $p=0.001$, $\eta_p^2=0.240$, as shown in Figure 12.8.

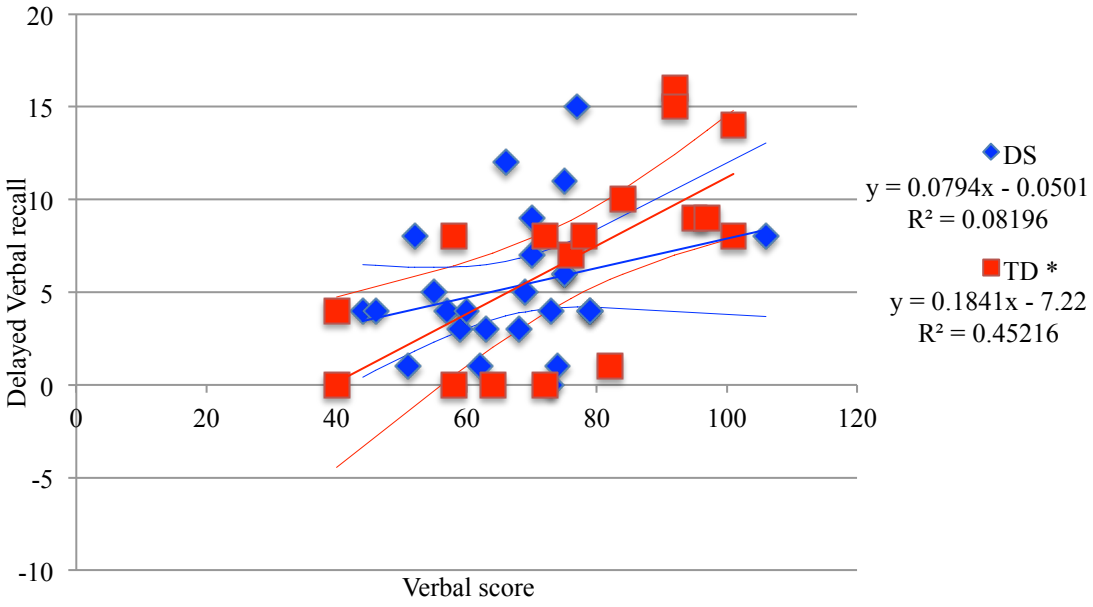

Figure 12.8 Delayed verbal recall over verbal score in DS and TD groups, CI represent 95%

APPENDIX C

Digit span memory

The goodness of fit of this model was considerable, (R^2=0.750) and explained a significant proportion of the variance observed, $F(3,60)=59.95$, $p<0.001$, $\eta_p^2=0.750$. The performance at youngest CA assessed was significantly different between groups, $F(1,60)=14.93$, $p<0.001$, $\eta_p^2=0.199$. With the groups combined, CA significantly predicted performance on this task, $F(1,60)=20.22$, $p<0.001$, $\eta_p^2=0.252$. However, these main effects should be interpreted with caution as there was also a significant interaction between CA and performance between groups, $F(1,60)=8.17$, $p=0.006$, $\eta_p^2=0.12$, with the DS group improving at a fifth the rate of the TD group (DS: 0.023, TD: 0.103). The performance disparity at onset was 9 points, as shown in Figure 12.9.

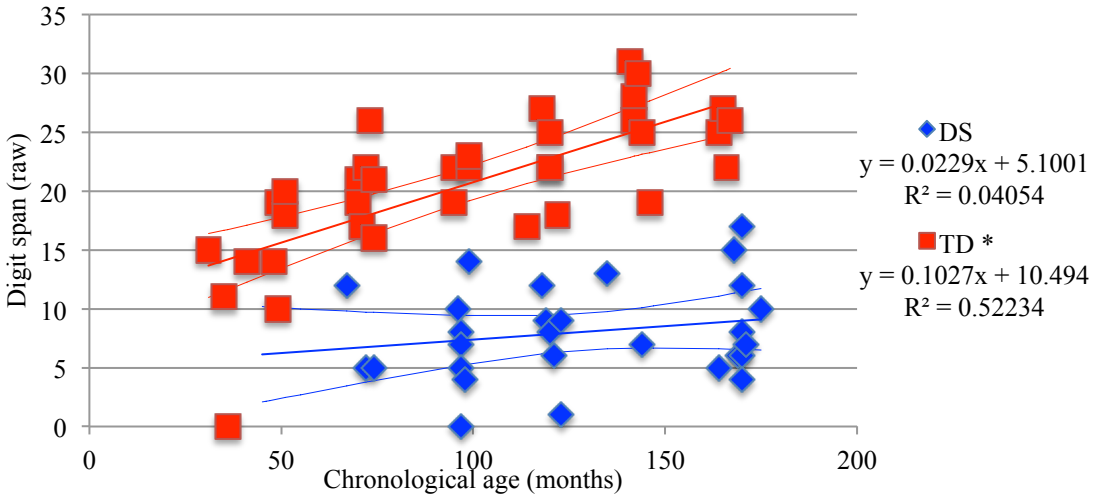

Figure 12.9 Raw digit span over CA in DS and TD groups, CI represents 95%

APPENDIX C

Examining performance over verbal score and using only TD participants who fall within the same range of distributions as the DS group, the results were as follows. The goodness of fit of the model was lower than in the CA or overall MA model (R^2=0.555). Group did not significantly affect performance at onset, $F(1,37)=2.73$, $p=0.107$, $\eta_p^2=0.069$. MA significantly modulated task performance across groups, $F(1,37)=16.54$, $p<0.001$, $\eta_p^2=0.309$. The relationship between digit span and verbal score improved similarly in the two groups, $F(1,37)=0.09$, $p=0.763$, $\eta_p^2=0.002$, as shown in Figure 12.10.

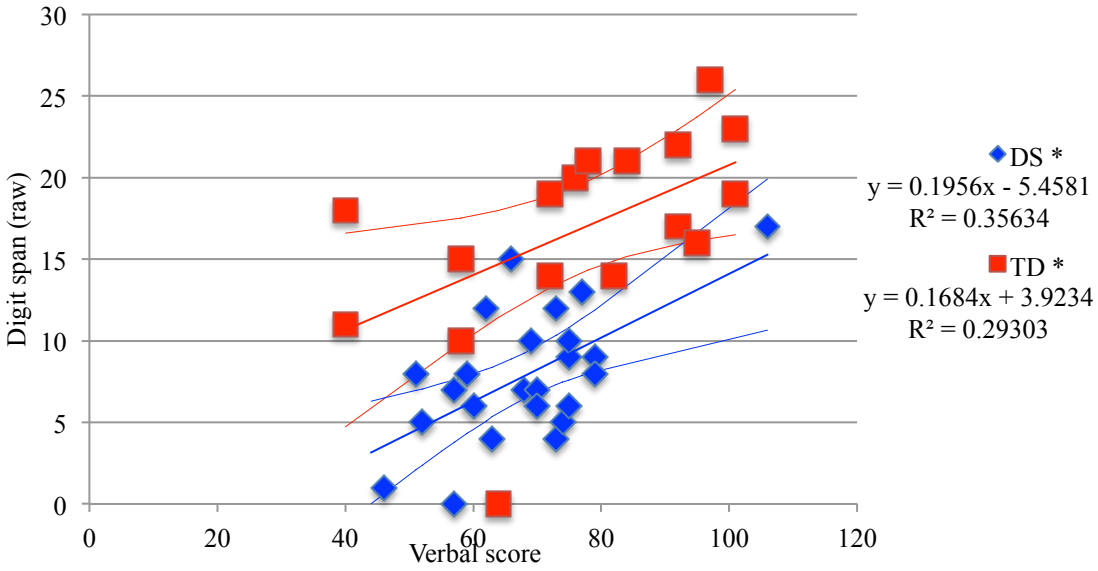

Figure 12.10 Digit span over verbal score in DS and TD groups, CI represent 95%

Verbal Fluency

The goodness of fit of this model was considerable (R^2=0.741) and explained a significant proportion of the variance observed, $F(3,70)=66.69$, $p<0.001$, $\eta_p^2=0.741$. The performance at youngest CA assessed was not significantly different between groups, $F(1,70)=3.65$, $p=0.060$, $\eta_p^2=0.05$. With the groups combined, CA significantly affected performance on this task, $F(1,70)=86.33$, $p<0.001$, $\eta_p^2=0.552$. However, this should be interpreted with caution as there was also a significant interaction between CA and performance on this task between groups, $F(1,70)=30.11$, $p<0.001$, $\eta_p^2=0.301$. The DS group improved at a quarter of the rate of the TD group (DS: 0.042, TD: 0.164), as shown in Figure 12.11.

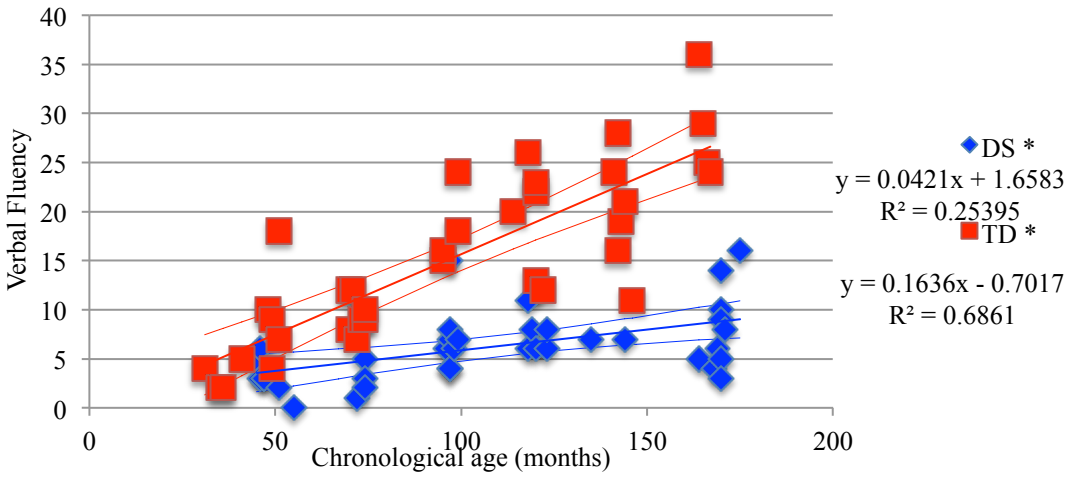

Figure 12.11 Verbal fluency over CA in DS and TD groups, CI represents 95%

APPENDIX C

Examining performance over verbal score and using only TD participants who fall within the same range of distributions as the DS group, the results were as follows. The goodness of fit of the model was lower than in the CA or overall MA model (R^2=0.405). Group did not significantly alter performance at onset, $F(1,38)=0.75$, $p=0.387$, $\eta_p^2=0.020$. MA significantly modulated task performance across groups, $F(1,38)=11.37$, $p=0.002$, $\eta_p^2=0.230$. The relationship between verbal fluency and verbal score was not significantly different in the two groups, $F(1,38)=1.09$, $p=0.304$, $\eta_p^2=0.028$, as shown in Figure 12.12.

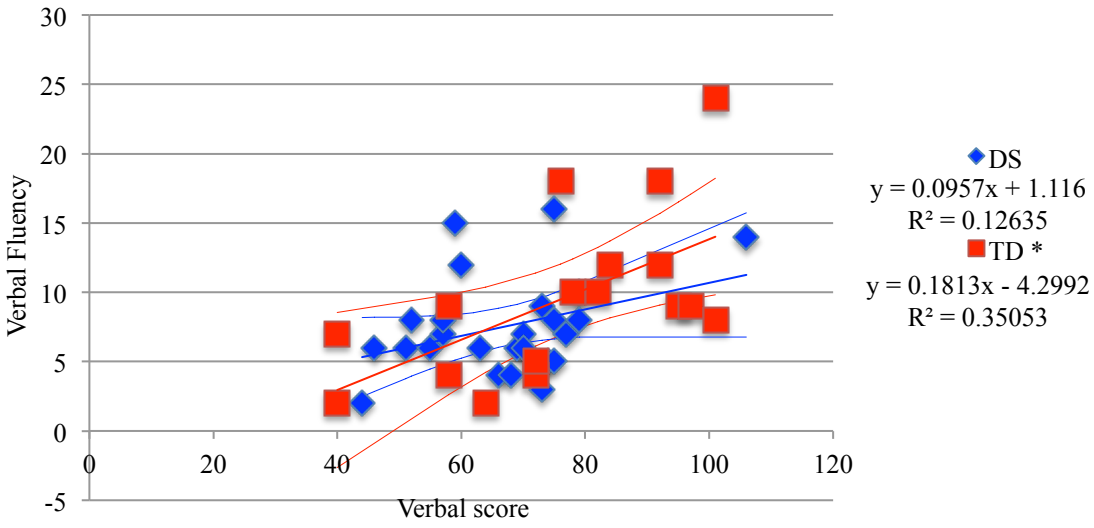

Figure 12.12 Verbal fluency over verbal score in DS and TD groups, CI represent 95%

APPENDIX C

Associative memory

Immediate associative memory

The goodness of fit of this model was moderate (R^2=0.153), but still explained a significant amount of the variance observed, $F(3,61)=3.67$, p=0.017, η_p^2=0.153. The performance at youngest CA assessed was not significantly different between groups, $F(1,61)=0.50$, p=0.482, η_p^2=0.008. With the groups combined, CA did not significantly predict performance on this task, $F(1,61)=3.51$, p=0.066, η_p^2=0.054, there was no significant interaction between CA and performance on this task between groups, $F(1,61)=1.50$, p=0.226, η_p^2=0.024, as shown in Figure 12.13.

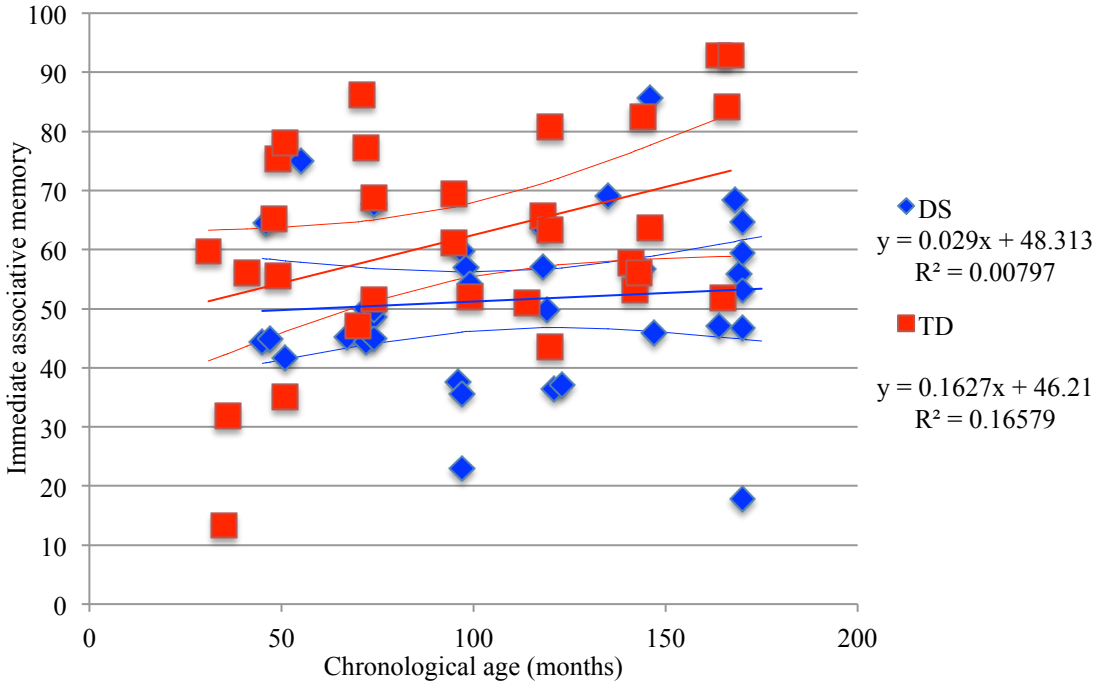

Figure 12.13 Immediate associative memory over CA in DS and TD groups, CI represent 95%

Delayed associative memory

The goodness of fit of this model was moderate (R^2=0. 172), but again explained a significant amount of the variance observed, $F(3,58)=4.03$, $p=0.011$, $\eta_p^2=0.172$. The performance at youngest CA assessed was not significantly different between groups, $F(1,58)=3.61$, $p=0.063$, $\eta_p^2=0.059$. With the groups combined, CA significantly predicted performance on this task, $F(1,58)=7.54$, $p=0.008$, $\eta_p^2=0.115$. Development of delayed associative memory abilities over CA was similar between groups, $F(1,58)=0.27$, $p=0.606$, $\eta_p^2=0.005$, as shown in Figure 12.14.

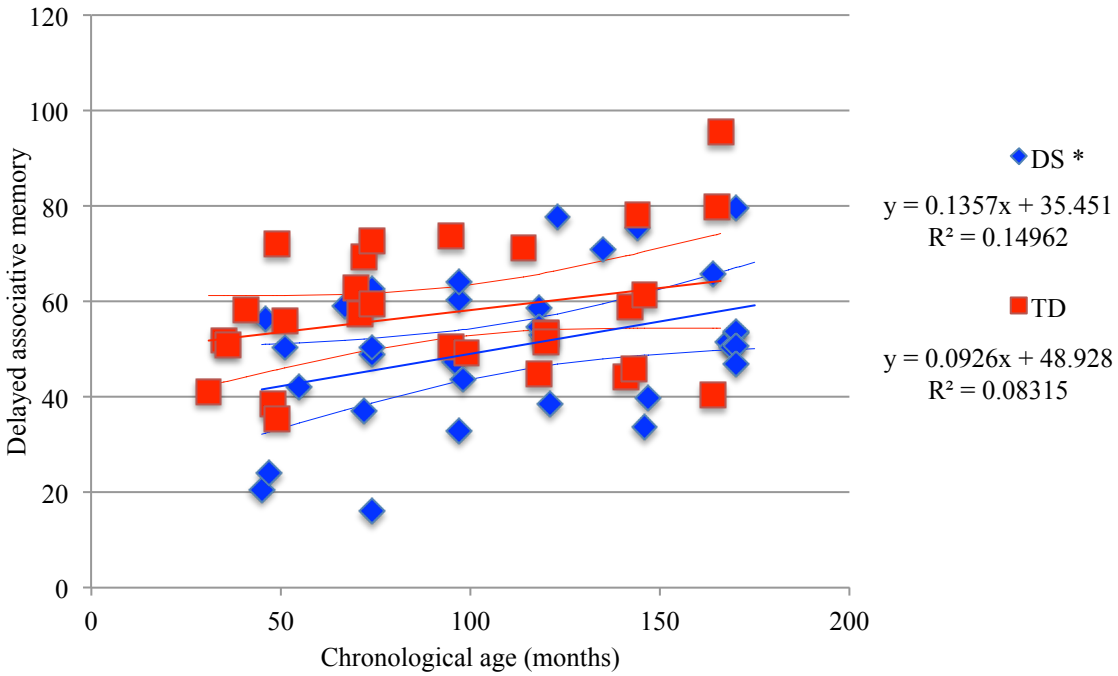

Figure 12.14 Delayed associative memory over CA in DS and TD groups, CI represents 95%

APPENDIX C

Within group within format task comparisons

In this section, tasks assessing abilities within memory formats are compared within the DS group over CA.

Visuospatial memory

The DS group did not perform significantly differently on the memory for object and object in place tasks, $F(1,30)=1.32$, $p=0.260$, $\eta_p^2=0.042$. CA did not significantly affect performance at onset ($F(1,29)=0.83$, $p=0.369$, $\eta_p^2=0.028$), and the groups did not improve at significantly different rates, as shown in Figure 12.15, ($F(1,29)=0.65$, $p=0.427$, $\eta_p^2=0.022$). This comparison was included for consistency, but since the object-in-place task failed to measure the target cognitive ability, this comparison does not yield meaningful interpretations.

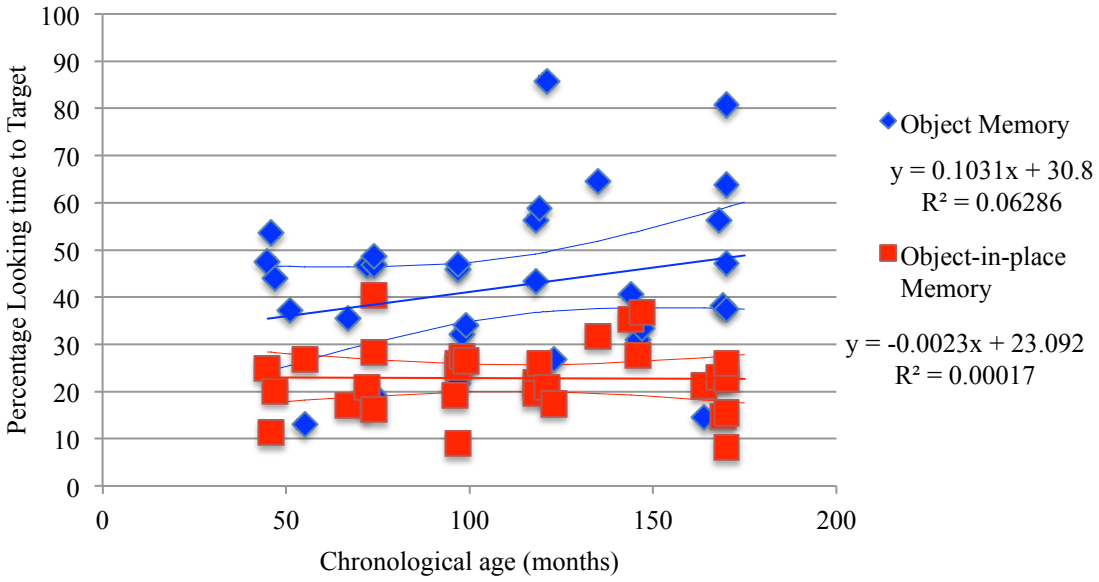

Figure 12.15 Object and object-in-place proportional looking time to target over CA in the DS group, CI represents 95%

APPENDIX C

Overall, the DS group performed significantly differently on immediate and delayed spatial recall, $F(1,23)=7.69$, $p=0.011$, $\eta_p^2=0.251$. This appears to be driven by a higher mean performance in the immediate (M=20.6), than the delayed spatial trial (M=11.46). CA did not significantly affect performance at onset, $F(1,22)=0.31$, $p=0.586$, $\eta_p^2=0.014$. Immediate and delayed spatial abilities developed at significantly different rates over CA in the DS group ($F(1,22)=4.93$, $p=0.037$, $\eta_p^2=0.183$), as shown in Figure 12.16. Delayed spatial recall is subject to large floor affect, which could skew the interpretation of these data.

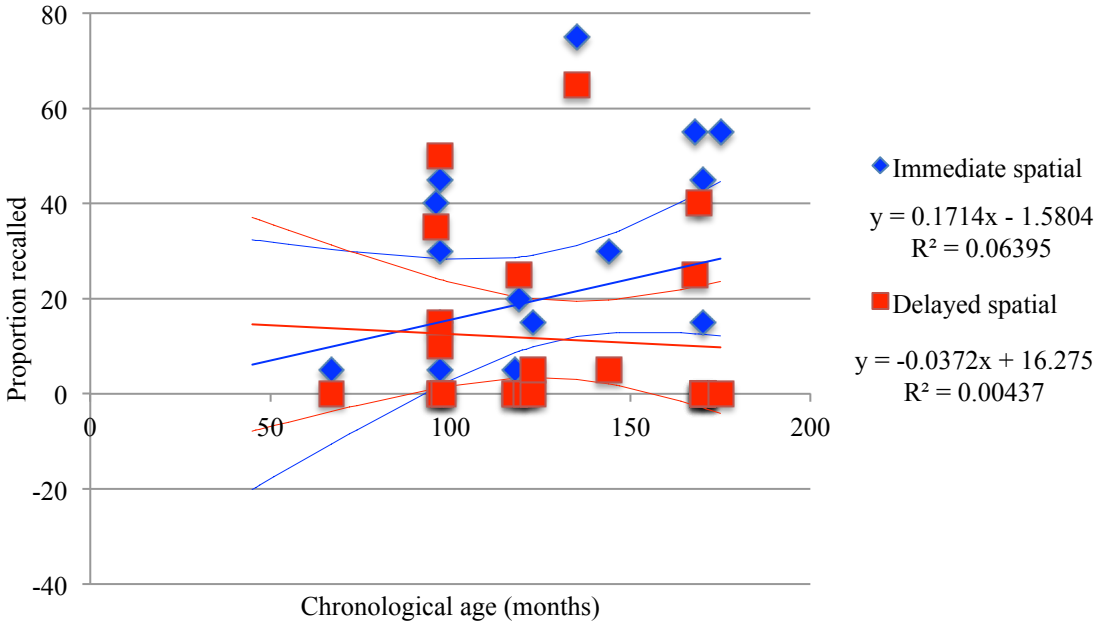

Figure 12.16 Immediate and delayed spatial memory over CA in the DS group, CI represents 95%

APPENDIX C

Verbal memory

The DS group did not perform significantly differently on immediate and delayed verbal recall, $F(1,30)=1.23$, $p=0.276$, $\eta_p^2=0.039$. CA significantly affected performance at onset ($F(1,29)=10.11$, $p=0.003$, $\eta_p^2=0.259$. There was a borderline significant interaction between task performance and CA ($F(1,29)=4.09$, $p=0.052$, $\eta_p^2=0.124$, implying the task abilities improved similarly with age, but were almost significantly different, as shown in Figure 12.17. This appears to be driven by delayed verbal recall improving at twice the rate of immediate verbal recall.

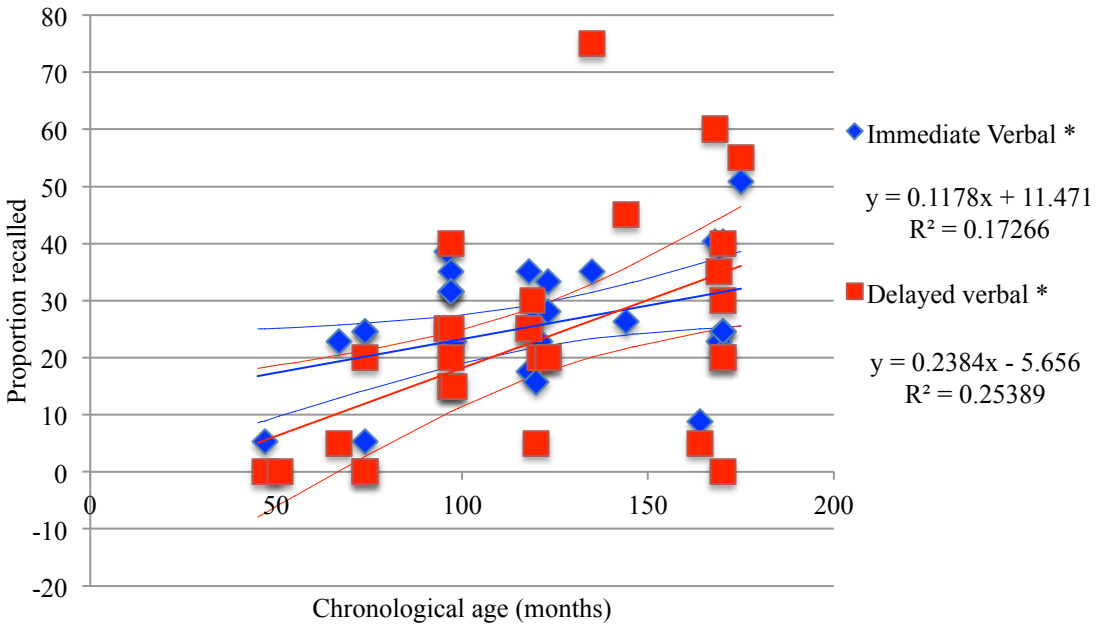

Figure 12.17 Immediate and delayed verbal memory over CA in the DS group, CI represents 95%

APPENDIX C

Associative memory

The DS group performed non-significantly differently on immediate and delayed associative memory, $F(1,32)=0.52$, $p=0.477$, $\eta_p^2=0.016$. CA did not significantly affect performance at onset, $F(1,31)=4.02$, $p=0.054$, $\eta_p^2=0.115$. Immediate and delayed associative memory developed similarly over CA in the DS group, ($F(1,31)=1.58$, $p=0.218$, $\eta_p^2=0.048$), as shown in Figure 12.18.

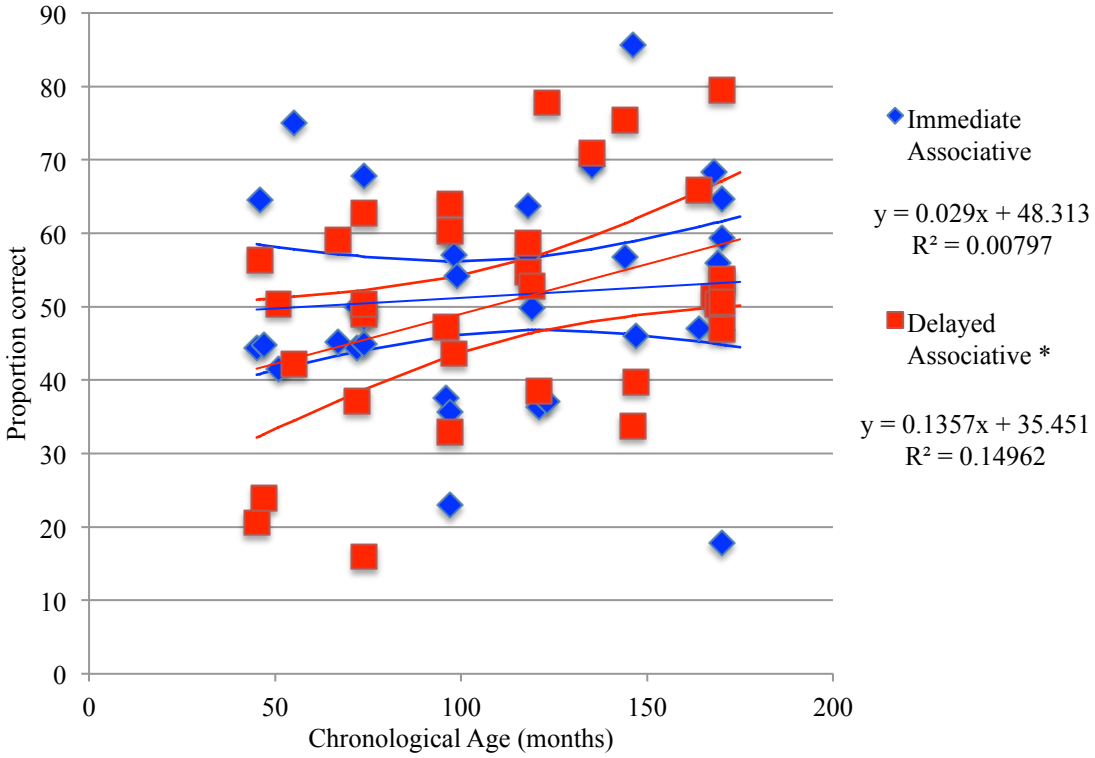

Figure 12.18 Immediate and delayed associative memory over CA in the DS group, CI represents 95%

APPENDIX C

Between group between task comparisons

In this section, all tasks assessing a specific format of memory are compared between groups. As the relationship between DS and TD abilities have already been characterised, as have the relationships between the variables in the DS group over development, these are not discussed here. The only relevant outcome of these analyses is the group by age-group by task interaction. This reveals if the relationship between the dependent variables over CA or MA are comparable between groups.

Visuospatial memory

There was not a significant difference in the relationship of immediate and delayed visuospatial recall across CA between groups, $F(1,56)=2.34$, $p=0.132$, $\eta_p^2=0.04$, as shown in Figure 12.19.

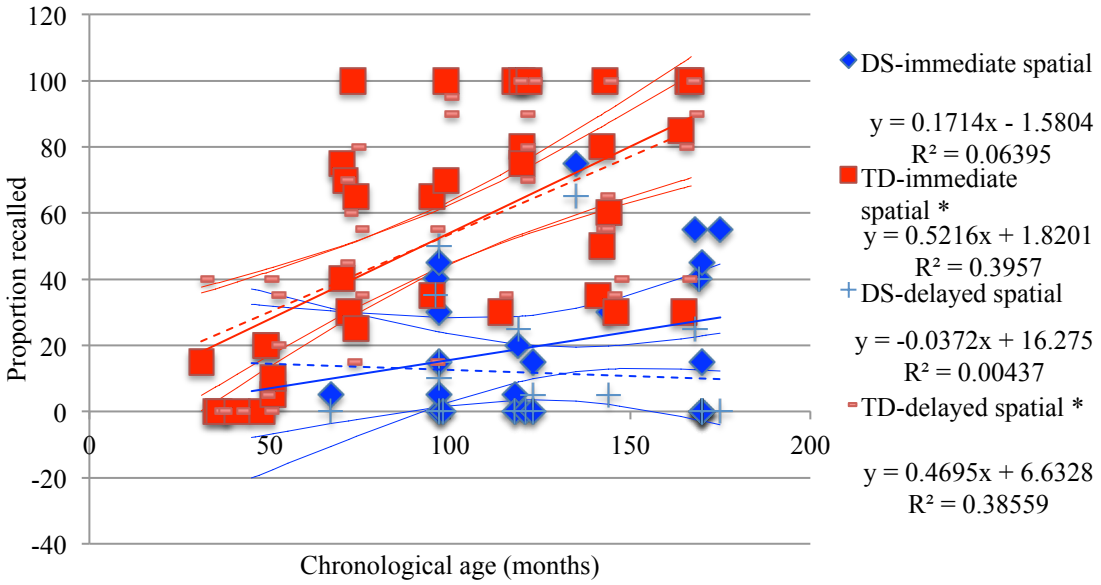

Figure 12.19 Proportional immediate (solid) and delayed (dashed) spatial recall in DS and TD groups over CA, CI represents 95%

APPENDIX C

Verbal memory

Examining abilities over CA, there was not a significant difference in the relationship between tasks by group, as shown in Figure 12.20, $F(1,63)=0.33$, $p=0.570$, $\eta_p^2=0.005$.

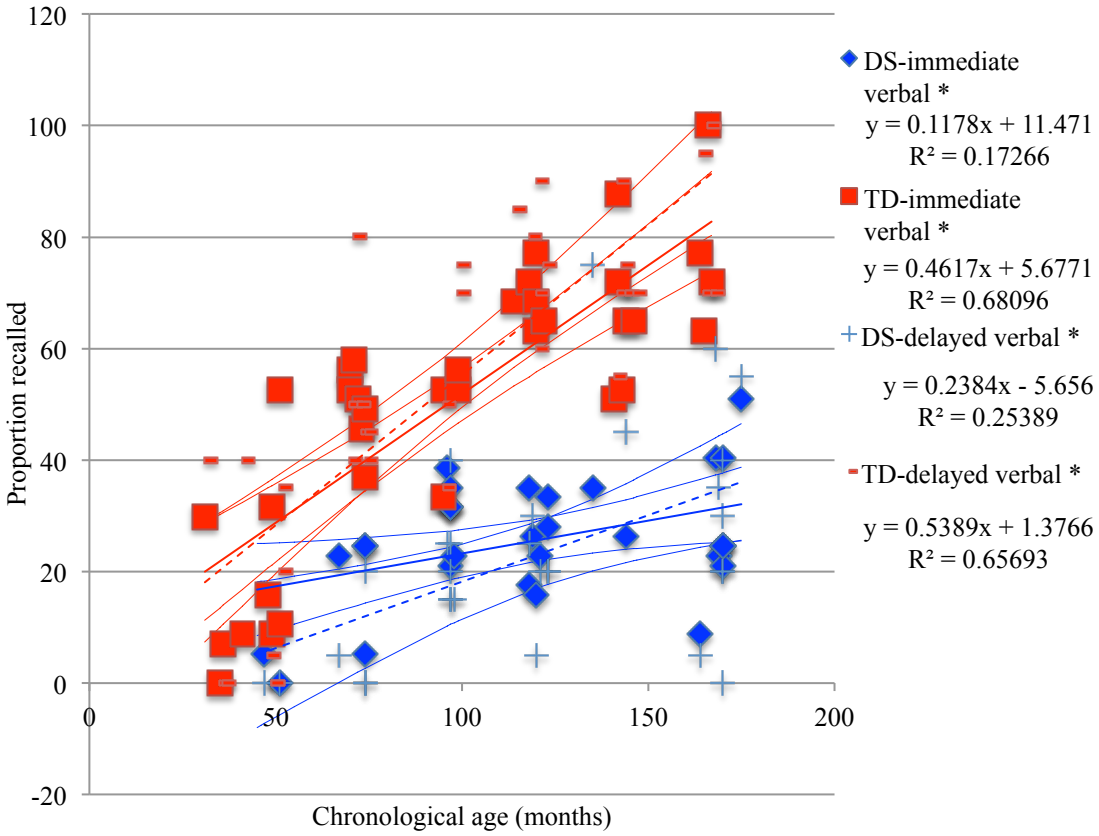

Figure 12.20 Proportional immediate (solid) and delayed (dashed) verbal recall in DS and TD groups over CA, CI represent 95%

APPENDIX C

When only including those individuals with overlapping verbal scores and examining performance over verbal score, there was not a significant different in the relationship between tasks by group, as shown in Figure 12.21, $F(1,38)=0.12$, $p=0.731$, $\eta_p^2=0.003$.

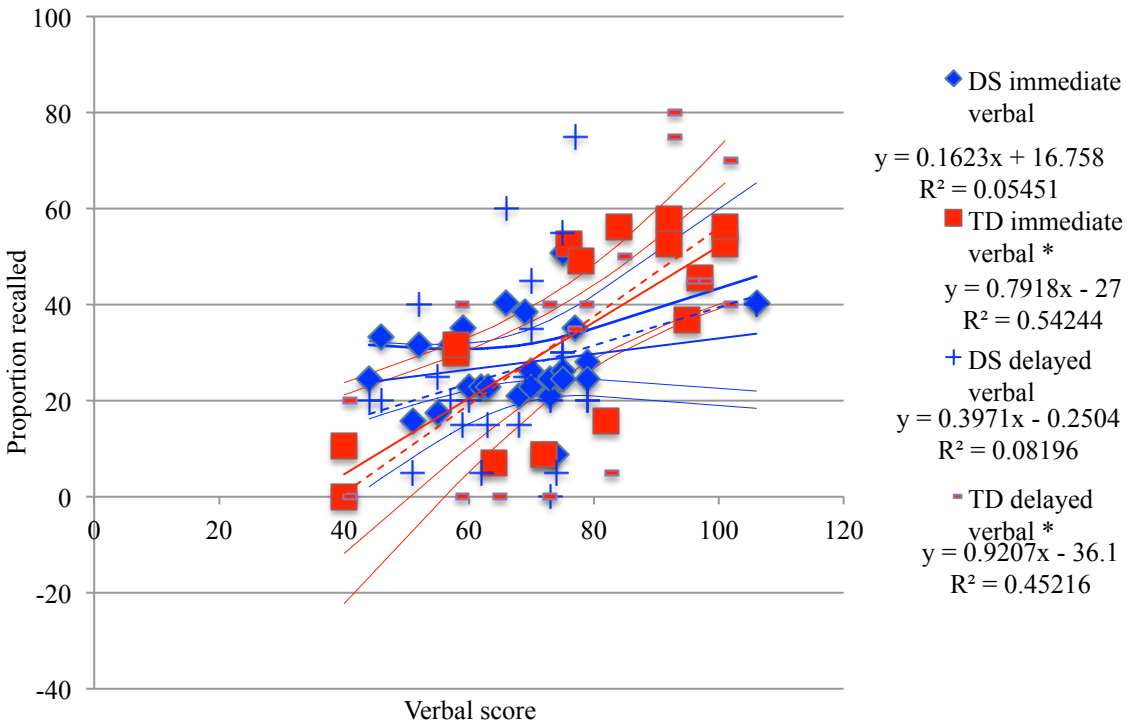

Figure 12.21 Proportion immediate and delayed verbal recall in DS and TD groups over verbal score, CI represents 95%

APPENDIX C

Associative memory

Examining associative memory abilities over CA, there was not a significant difference in the relationship between tasks by group, as shown in Figure 12.22, $F(1,58)=2.11$, $p=0.152$, $\eta_p^2=0.035$.

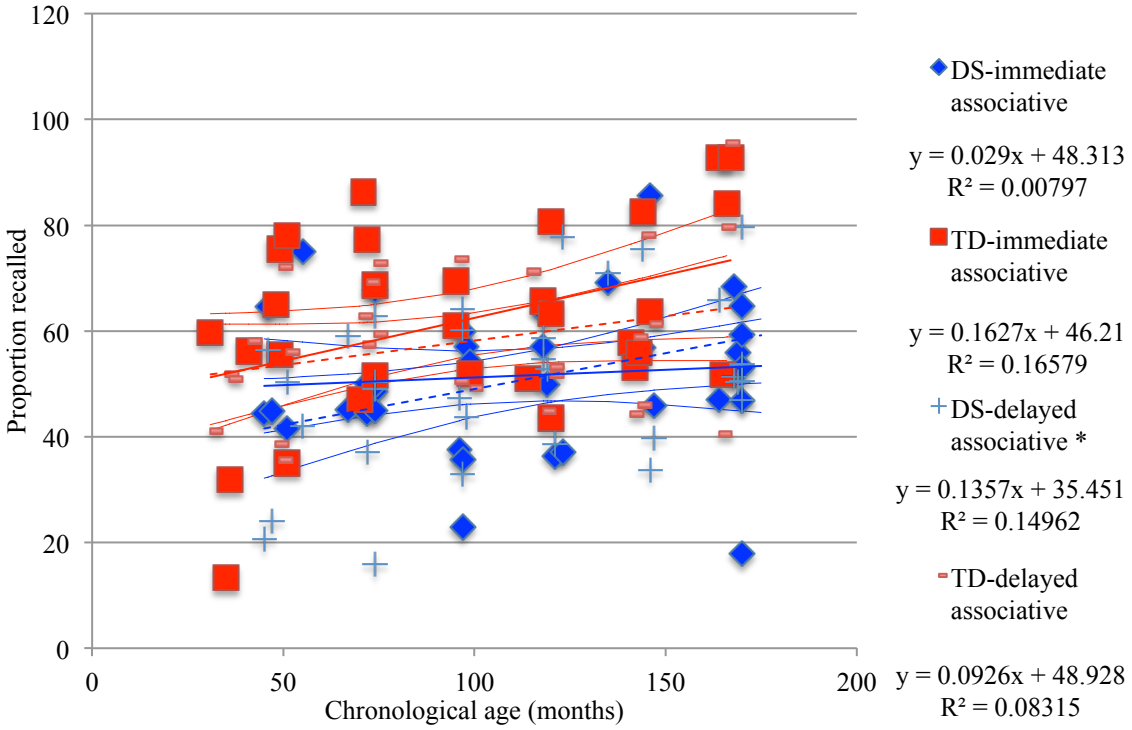

Figure 12.22 Proportion immediate (solid) and delayed (dashed) associative memory correct in DS and TD groups over CA, CI represents 95%