COGNITIVE ASSESSMENT OF PAEDIATRIC NEURODEGENERATIVE DISEASE

by

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Abstract

Inherited metabolic diseases (IMDs) are a large class of heterogeneous genetic disorders caused by dysfunction within a single pathway of intermediary metabolism. In many of these diseases, the dysfunction of metabolic enzymes leads to the accumulation of toxic metabolites which disrupts the normal development of the central nervous system. With the advent of treatments that positively influence neuropsychological outcomes, there is a need for sensitive and objective neuropsychological measures that allow patients to be systematically tracked in order to understand the efficacy of existing treatments.

In this thesis, a neuropsychological test battery consisting of attention, language and oculomotor measures was developed to accurately describe individual and developmental differences between IMD patients and healthy developing controls. The functioning of five diseases was examined: Morquio syndrome (N = 12), Hurler syndrome (N = 3), Maroteux-Lamy syndrome (N = 2), Tyrosinemia type I (N = 13) and Tyrosinemia type III (N = 5). Findings indicated that disease effects were not homogeneous across tasks, and that performance on the same tasks was not uniform across diseases. The obtained data offers a promising basis for understanding how biological factors influence the severity and timecourse of developmental effects in future research.

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1.0 INTRODUCTION

Inherited metabolic diseases (IMD's) are large class of heterogeneous genetic disorders that are caused by dysfunction within a single pathway of intermediary metabolism. For the majority of these diseases it is the dysfunction of metabolic enzymes that leads to the accumulation of toxic metabolites, which disrupts the normal development of the central nervous system. Depending on the specific role of the dysfunctional enzymes, the severity of symptoms associated with IMDs can vary widely. Mild symptoms can include physiological abnormalities such as skeletal dysplasia and impaired endurance (Davison, Kearney, & Horton, 2012; Wraith, 2006), while severe consequences can include mental retardation, central nervous system (CNS) complications, and reduced life expectancy (Bendadi et al., 2014a; De Laet et al., 2011; Masurel-Paulet et al., 2008; Thimm et al., 2011, 2012).

To date there has been abundance of animal-model and genetic research detailing the biological and genetic factors that relate to inherited metabolic disease (IMD) (Leonard, 2006; Wendel & Baulny, 2006; Wraith, 2006). In comparison, neuropsychological research into the cognitive development of IMDs has been limited to standardised intelligence tests, achievement tests and adaptive behaviour scales (Bax & Colville, 1995; Biernacka, Jakubowska-Winecka, & Tylki-Szymanska, 2010; Davison et al., 2012; Shapiro et al., 2009) that are not always suitable or the tracking of the impact of disease progression upon neuropsychological function (Martin et al., 2008). In particular, it is unclear how disease progression across IMDs affects cognitive function; does cognitive function decline globally or are specific cognitive domains affected more severely than others? The lack of research in this area is surprising considering the emergence of interventions (enzyme replacement therapy, haematopoietic stem cell transplantation) over the past decade that are able to stabilise symptoms and extend the life expectancy of patients (Desnick & Banikazemi, 2006; Eapen et al., 2007; Escolar et al., 2005; Patterson, Vecchio, Prady, Abel, & Wraith, 2007).

Consequently, there is a demand for measures of cognitive function that are able to accurately and objectively track the natural progression of IMDs, which can evaluate the efficiency of therapeutic interventions, and can inform clinicians and researchers which therapies produce the best cognitive outcomes for patients.

To our knowledge no set of neuropsychological measures exists that are tailored towards IMD populations; this is mainly due to the unavailability of a commercial source that utilises a "toolkit" approach and also to the complex heterogeneous nature of these diseases. This is surprising since the combined prevalence of IMDs is 1 in 784 live births within the West Midlands (Sanderson, Green, Preece, & Burton, 2006). In addition, a greater number of IMDs are now being included in neonatal screening programs (Marsden & Levy, 2010) so detailed longitudinal tracking of these diseases is important. Thus, the current project aims to be the first to develop a sensitive and efficient battery of neuropsychological tests that is specifically tailored to measure the functional capabilities of children with rare inherited metabolic diseases. To achieve this, the project will focus on developing tasks that assess the cognitive abilities of language, motor control and attention in order to assess how the diseases selectively or generally disrupts cognitive abilities as a result of disease progression.

The rationale for the selection of tasks was based upon several criteria. Firstly, due to the rarity of these disorders, early formulation of tasks was based upon input from clinically collaborators to select domains of cognitive function where impairments are suggestive of metabolic disease. For example, disruption of the oculomotor system (vertical and horizontal gaze palsy) is pathognomic of several metabolic disorders oculomotor symptoms (Niemann-Pick Type C and Gaucher's disease), while attention and language deficits are common features in other metabolic diseases (Hurler Syndrome and Tyrosinemia I respectively). Secondly, tasks needed to be sensitive to developmental change across a wide age range and be influenced minimally by floor or ceiling effects. This was particularly important in order

to identify mild and substantially cognitive impariments in patient groups, since a primary outcome of this work is to produce measures which could potentially screen for neurological symptoms. For this reason I focused on including tasks (e.g. visual search task, non-word learning task, saccadic eye movement), which have been successfully employed in neuropsychological research to examine both cognitive development across a wide age range and cognitive impairments in very young patient populations (T. J. Anderson & MacAskill, 2013; Brenner, Turner, & Müller, 2007; Gray, 2004; Hommel, Li, & Li, 2004a; Karatekin, 2007). In addition, I intended to minimise the influence of ceiling and floor effects by employing several tasks which produced reaction times as outcome measures. This is because reaction times continue to provide a measure developmental change even after response accuracy levels are at ceiling (Thomas, Annaz, & Ansari, 2009). Finally, standardised measures (British Picture Vocabulary Scale) were included to yield mental age equivalent scores that would allow a more detailed description of cognitive dysfunction in the future analysis of this work.

Ultimately, it is hoped that the test battery can meet the clinical need for an instrument that can be used to accurately track disease progression, provide a sensitive means to evaluate positive and negative outcomes of therapeutic interventions, and can fulfil the research need for information on the specific impact of neurodevelopmental disorders on language, motor control and attention.

The work described in this thesis is considered to make an original contribution to the body of knowledge involving the cognitive function of children diagnosed with an IMD by answering the following principle questions:

(i) What are the best measures (most sensitive and efficient) to use to track disease progression during different stages of the disease?

(ii) Does the functioning ofspecific cognitive domains develop/decline differently along the time course of a disease?

(iii) What is the homogeneity across and within diseases for the cognitive areas that are most and least affected by disease?

2.0 LITERATURE REVIEW

2.1 Introduction

A broad set of research areas are integrated to form the theoretical background for the research reported in this thesis. In brief, the subject matter can be considered to fall into two areas: 1) cognitive profiles of inherit metabolic disorders (IMDs), and 2) models and methods associated with the development of attention, language, and oculomotor function. In the case of cognitive function in IMD, the vast majority of the literature does not relate study findings to models of cognitive development. For this reason, in documenting this literature survey the two areas have been categorically organised into separate bodies of review.

The first section of the review covers IMD cognitive function, describing the clinical features with the inclusion of a description of relevant findings from studies detailing the intellectual function. In addition, the section explores known cortical abnormalities discovered through imaging techniques and attempts to link them to cognitive dysfunction. In the second section, models and methods of three cognitive domains (attention, language, and oculomotor function) are described in depth. Studies reviewed in this section discuss established methodologies and include a discussion of cortical areas associated with each cognitive domain. Finally, evidence from neurological disorders will be integrated to illustrate how these methodologies have been used to investigate cognitive dysfunction.

The purpose of this literature survey is to firstly, describe the cognitive profiles of specific IMDs and the homogeneity of cognition within and across disorders and, secondly, to describe neuropsychological methods commonly employed with neurological and developmental disorders that have received substantial research attention.

2.2 Inherited Metabolic Diseases

Inherited metabolic diseases are a complex heterogeneous group of genetic disorders that result from the dysfunction of one or more metabolic enzymes that are necessary for normal central nervous system development (Martins, 1999). This first section of the literature survey introduces a number of these diseases: lysosomal storage diseases (specifically muccopolysaccharide disorders) and inborn errors of amino acid metabolism (specifically Tyrosinemias). Evidence will be presented from materials and papers that describe the clinical presentation, neurological symptoms, and any known brain anatomy found through positron emission tomography (PET) or magnetic resonance imaging (MRI). Disorders discussed here are grouped according to the metabolic basis of the disease.

2.2.1 Lysosomal Storage Diseases (Mucopolysaccharide Disorders)

Lysosomal storage diseases are a group of chronic, progressive multisystem disorders caused by dysfunctional lysosomes within cell bodies (Wraith, 2006). Here we will review several lysosomal storage diseases categorised as mucopolysaccharide diseases (MPS diseases, also termed glycosaminoglycans (GAGs)). MPS diseases are caused by the deficiency of degradative enzymes that are required to break down specific mucopolysaccharides within lysosomes. Eleven distinct MPS disorders are known to exist that are each caused by specific enzyme deficiencies (Neufeld & Muenzer, 2001). Inheritance of these disorders is autosomal recessive for all except MPS-II (Hunter's syndrome), which is an X-linked recessive disorder, while epidemiological data (Brown, 2011) report the prevalence of these disorders ranges from 1 in 100,000 to 1 in 600,000 live births.

There are several shared clinical features among the eleven identified MPS disorders. Severe symptoms range from neurological abnormalities, bone dysplasia, hepatosplenomegaly, and facial dysmorphism, to developmental regression and reduced life

expectancy. Conversely, in the more attenuated MPS disorders patients can present with an almost normal clinical phenotype and life span (Wraith, 2006).

A description of three MPS diseases that are investigated in the current project is given below which include: Hurler/Hurler-Scheie syndrome (MPS IH/IHS); Morquio Disease (MPS IV); and Maroteaux-Lamy syndrome (MPS VI).

Hurler / Hurler-Scheie Syndrome (MPS-IH/IS)

MPS-I is caused by the deficiency of the enzyme α-L-iduronidase which in turn leads to the accumulation of dermatan and heparin sulphate. MPS-I has an incidence of 0.61-1.30 per 100,000 live births (Moore, Connock, Wraith, & Lavery, 2008). Elevated levels of these glycosaminoglycans (GAGs) in tissue produces psychomotor retardation, respiratory and cardiac complications, and impaired vision and hearing, and cardiac complications (Neufeld & Muenzer, 2001; Wraith, 2006). Presentation of short stature, cardiac disease, corneal clouding, facial dysmorphia, and hepatosplenomegaly are common symptoms that appear in the second and third years of life. The severity of these symptoms occupies a wide continuum across individual cases of MPS-I, with the most severe cases being detected during the first year of life; typically presenting with skeletal deformities and endocardial fibroelastosis (Stephan et al., 1989). In these cases developmental delay is apparent by 12-24 months and the maximal functional age is typically around 2 to 4 years (Neufeld & Muenzer, 2001). In contrast the less severe cases of MPS-I are characterised by normal intelligence, normal height and life expectancy, with a likelihood of disability from joint stiffness and cardiac valve lesions (Wraith, 2006). On the basis of the severity of the disease manifestations, MPS-I can be divided into 3 disease subtypes. These subtypes include, in order of most to least severe, Hurler (MPS-IH), Hurler-Scheie (MPS-IHS), and Scheie (MPS-IS) subtypes.

Treatment of MPS-I includes enzyme replacement therapy (ERT), which can elevate the majority of the disease manifestations (Moore et al., 2008; Wiseman et al., 2013) but has no impact on neurological complications since ERT is unable to by-pass the blood-brain barrier. Another form of treatment is allogenic haematopoietic stem cell transplantation (HSCT) that has been reported to significantly improve functional outcomes and life expectancy (Aldenhoven, Boelens, & de Koning, 2008; Neufeld & Muenzer, 2001; Shapiro et al., 2009).

The neurological signs of MPS I are progressive learning difficulty, fatigue, developmental regression, and hydrocephalus. In addition, patients may present with hearing loss as a result of conductive and sensorineural problems. Vision impairment is common due to optic nerve head swelling with atrophy (Müller-Forell, Schulze Frenking, Amraoui, & Beck, 2007). The development of cognitive function of MPS-I patients has been investigated over the past decade as a means to measure the impact of HSCT. A review of 10 children following HSCT (Shapiro et al., 2009) revealed deficits in attention and executive functions, lower than average verbal IQ, and normal memory. Results from this study also showed that the rate of cognitive decline increased with the age at which the patients received the HSCT procedure. Other research has examined the effect of ERT in preventing nervous system degradation (Biernacka et al., 2010) by measuring IQ using the Psyche Cattell Infant's Intelligence Scale. Here children with MPS-I were found to have a measurable decrease in IQ and rate of new skill learning with advancing age. Despite these findings, the majority of research identifies the need for a more accurate measure to distinguish the cognitive development of the disorder (Biernacka et al., 2010) due to the limitations of current standardised measures in longitudinal disease tracking (Martin et al., 2008).

Neuroimaging features of MPS IH patients typically include diffuse white matter changes in the periventricular white matter (Seto et al., 2001). It is believed that these

changes may reflect delayed myelination or progressive demyelination through the course of the disease (Müller-Forell et al., 2007) that contribute to developmental regression in MPS-I (Gabrielli et al., 2004). Another commonly reported neuroimaging feature of MPS-I is cerebral atrophy, specifically the widening of the cortical sulci and inter-hemispheric fissure (Matheus et al., 2004).

Morquio Syndrome (MPS-IVa)

Morquio syndrome (MPS-IVa) is caused by the defiency of the enzyme N-acetylgalactosamine-6-sulfase which has a role in the sequential degradation of keratan sulphate and chondroitin-6-sulfate (Neufeld & Muenzer, 2001; Wraith, 2006). Keratan sulphate chronically and progressively accumulates within connective tissue, including the cornea, cartilage and heart valve (Hendriksz et al., 2013). Subsequently, patients present with severe skeletal dysplasia, hip dysplasia, marked short stature, genu valgum, and cornea clouding (Hendriksz et al., 2013; Wraith, 2006). Like other MPS disorders treatment can include ERT and HSCT as a means to alleviate the majority of the skeletal and coronary complications.

In contrast to other MPS disorders, MPS-IV patients are not reported to possess neurological or neurocognitive impairments (Dvorak-Ewell et al., 2010; Wraith, 2006). Though, recent research has suggested that MPS-IV patients could possess mild cognitive impairments in comparison to other MPS disorders. Davison et al. (2012) reviewed the performance of 14 MPS-IV children on a set of standardised IQ measures and found that 37% of the sample scored below the 78th percentile on a measure of full scale IQ. Additionally, parents of patients reported behavioural problems, highlighting several problems such as anxiety, attention and somatic complaints. The authors concluded that the presence of mild neurocognitive complications in children with MPS-IV is likely given the role of keratan

sulphate and chondroitin-6-sulfate in the coordination of neuroaxonal connection formation during foetal and neonatal brain development (Miller, Sheppard, & Pearlman, 1997).

Here, reported behavioural difficulties require further clarification; are these behaviour problems linked to an impairments of executive function, and how are the behavioural problems related to other domains of cognition? This is one research question that will be addressed in the current body of work.

Neuroimaging findings have reported an absence of neuroanatomical abnormalities within MPS-IV patients (Koto, Horwitz, Suzuki, & Tiffany, 1978). In contrast, animal model research (Tomatsu et al., 2008) has revealed abnormal storage materials in neurons and glia of the hippocampus. Furthermore, excess storage material can be cleared in mice with a high dose of ERT. Lastly, the neuropsychological assessment of MPS-IV patients conducted by Davison et al. (2012) observed mild neuroanatomical abnormalities in more than half the patients. Abnormalities included mild asymmetry of the lateral ventricles, prominent perivascular spaces, and high signal white matter areas of the right frontal lobe.

Maroteaux-Lamy Syndrome MPS VI

Maroteaux-Lamy Syndrome (MPS VI) is caused by a deficiency or dysfunction of the enzyme N-acetylgalactosamine- 4-sulfatase which is required for the degradation of dermatan –sulphate (Wraith, 2006). MPS VI has an estimated incidence ranging from 1 in 248,095 to 1 in 300,000 (Meikle, Hopwood, Clague, & Carey, 1999; Nelson, 1997; Sanderson et al., 2006) and patients usually either die in their teens or early 20s or may live into their 40s and 50s depending on the severity of disease progression (Giugliani, Harmatz, & Wraith, 2007). Similar to other MPS disorders, MPS VI is a clinically heterogeneous multisystem disorder (de Almeida-Barros et al., 2012; Giugliani et al., 2007; Wraith, 2006) with a variable age of onset. The most common complications associated with MPS VI are

structural due to the important role that dermatan-sulphate has within connective tissue. Consequentially, early presentations of MPS VI include reduced growth velocity, enlarged head and chest deformities (de Almeida-Barros et al., 2012; Giugliani et al., 2007). As the disease progresses, at approximately 2-3 years of age, emerging symptoms include coarse facial features, hepatosplenomegaly, joint stiffness, and heart and respiratory abnormalities (Azevedo et al., 2004). Typically MPS VI is not associated with any manifestations of progressive intellectual impairment, however the physical limitations of MPS VI are expected to indirectly produce delays in learning and motor skill development (Giugliani et al., 2007). The current body of work will be one of the first investigations of cognitive function in children diagnosed with MPS VI.

2.2.2 Tyrosinemia

Tyrosinemia is an inborn error of metabolism where the patient is unable to break down the amino acid tyrosine. Three different types of tyrosinemia exist (type I, II, and III), each classified by the deficiency of a specific enzyme within the tyrosine metabolic pathway (De Laet et al., 2011; Scott, 2006). All types of tyrosinemia are characterised by the accumulation of tyrosine in tissue and body fluids. Tyrosinemia-I is the most severe form of the three disorders in which patients present with progressive liver disease, painful neurologic crises, rickets and hepatocarcinoma (Bendadi et al., 2014a; Scott, 2006; Thimm et al., 2012). Tyrosinemia-II and III are more benign than tyrosinemia-I; the presentation of tyrosinemia-II is associated with hyperkeratotic plaques on the hands and soles of feet, and photophobia. Tyrosinemia-III patients present with a more variable phenotype, while neurological symptoms such as developmental regression and ataxia are common (Cerone et al., 1997; Ellaway et al., 2001).

Treatment of these disorders varies depending on the type of tyrosinemia. Tyrosinemia-II and III is typically managed with a controlled diet to ensure levels of

tyrosinemia are maintained at safe levels. However the more severe form, type-I, is presently treated with the administration of 2-nitro-4-trifluromethylbenzoyl (NTBC) which prevents the accumulation of toxic metabolites affecting liver function (Bendadi et al., 2014a). One documented side-effect of NTBC is the risk of developing mental retardation (Bendadi et al., 2014a; Masurel-Paulet et al., 2008; Thimm et al., 2012) at the cost of alleviating liver function complications.

Here, literature and materials describing the cognitive function and neural anatomy of patients diagnosed with tyrosinemia-I and III is reviewed. This will include literature that observes the impact of NTBC treatment on the cognition of tyrosinemia-I patients, and findings from reports on the cognition of tyrosinemia-III patients. An important research question for this group of disorders is to discover the heterogeneity of cognition among tyrosinemia-I and III patients. More specifically, does the treatment of NTBC with tyrosinemia-I patients produce a cognitive profile that is comparable to the cognitive profile of tyrosinemia-III patients?

Tyrosinemia Type-I

Tyrosinemia-I is an autosomal recessive disorder that results from the deficiency of fumarylacetoacetase, the final enzyme in the tyrosine metabolic pathway. Symptoms arise from the accumulation of fumaryl- and maleylacetoacetate, toxic agents that gather in body fluid and tissue. The range of clinical manifestations associated with tyrosinemia-I include hepatocellular carcinoma complications (Russo & O'Regan, 1990) and renal problems such as secondary rickets (Masurel-Paulet et al., 2008; Russo & O'Regan, 1990). The prevalence of tyrosinemia-I worldwide is rare. An occurrence of 1 in 100,000 live births has been reported (Scott, 2006).

Since 1992, NTBC has been used as an effective pharmacological treatment (Lindstedt, Holme, Lock, Hjalmarson, & Strandvik, 1992), prior to which the only curative procedure was liver transplantation. The function of NTBC is to replicate the metabolic block which occurs in tyrosinemia-III as a means to maintain levels of hepatotoxic metabolites (Thimm et al., 2012). Ultimately, the mechanisms of the tyrosine metabolic pathway in tyrosinemia-I patients are transformed into those of a tyrosinemia-III patient. However, progressive accumulation of tyrosine occurs as a side-effect of the NTBC drug (Lindstedt et al., 1992). Thus, patients are required to maintain a low tyrosine diet as part of the NTBC treatment (Lindstedt et al., 1992; Masurel-Paulet et al., 2008).

A growing body of research has investigated the long-term outcomes of tyrosinemia-I patients undergoing NTBC treatment. Recent studies have examined whether the possible toxicity of long-term NTBC use has an impact upon cognitive function (Bendadi et al., 2014a; De Laet et al., 2011; Masurel-Paulet et al., 2008; Thimm et al., 2012). A reoccurring finding has been that patients present with cognitive impairments later on in life, which is expected to be caused by elevated tyrosine levels that have not been sufficiently controlled with diet. For example, the study by Thimm et al. (2012) assessed the neurocognitive development of nine tyrosinemia-I patients using standardised psychometric tests. Here a high proportion of patients performed below normal on motor function, speech, and development. With regards to MRI findings, a study by Thimm et al. (2011) discovered an absence of neuroanatomical abnormalities in a sample of three tyrosinemia-I patients.

Tyrosinemia type-III

Tyrosinemia-III is an autosomal recessive disorder caused by the deficiency of 4-hydroxyphenylpyruvate dioxygenase, the second enzyme within the tyrosine metabolic pathway. This results in the accumulation and increased excretion of tyrosine. Unlike tyrosinemia-I, patients diagnosed with tyrosinemia-III have normal liver and renal function

(Ellaway et al., 2001; Scott, 2006). Despite this, several case studies (Cerone et al., 1997; D'Eufemia et al., 2009) have reported neurological impairments within tyrosinemia-III patients. The current treatment for tyrosinemia III patients consists of administration of ascorbic acid and a low-protein diet (Scott, 2006).

2.3 Models and Methods of Cognitive Development

Here models and methods from three areas of cognitive development are discussed: attention, language, and oculomotor function. For each domain, established models and methods, developmental trajectories, and findings from disorders groups are described.

2.3.1 Attention

The concept of attention (executive function) within psychology covers a broad set of functions: planning, attentional flexibility, error correction and detection, working memory, inhibitory control, and self-regulation (Welsh, Pennington, & Groisser, 1991; Zelazo, Carter, Reznick, & Frye, 1997). In the current thesis we will explore whether an attention deficit exists in any of the patient cohorts by employing a simple reaction time and visual search task.

The classic visual search paradigm captures the real life instances in which humans scan their visual environment to locate a visual target when presented with many different objects simultaneously. This might be when a child searches for their favourite toy from within a brimming toy box, or when a young adult tries to identify a friend whilst visiting a crowded bar. Both behaviours require the allocation of attention to specific visual features of the target whist inhibiting irrelevant visual features. Search will be deemed to be easy if the target can be identified based only on a single feature (feature search; perhaps the friend at the bar has a particularly unique hair colour). Search requires more attentional effort if

success depends on the combination of visual features (conjunction search; the child's favourite toy is a red ball that is among greens balls and red building blocks). Consequently, unlike feature search, conjunction search time increases linearly with the number of distractors in the visual scene (Duncan & Humphreys, 1989; Wolfe, 1998).

The Feature Integration theory (Treisman & Gelade, 1980) proposes the existence of two distinct mechanisms that enable accurate searching behaviours. First, a parallel search mechanism efficiently processes feature maps (e.g. colour, orientation, etc) of the visual scene in parallel. In a sense, this process enables the visual target to "pop-out" among distractors, thus negating the frequency of distractors. The second mechanism of visual search is a serial search mechanism, whereby the target is located through the conjunction of separate feature maps. In other words, no one feature map can be inspected to find the target. Here successfully locating a target requires the participant to sequentially shift attention from one search item to the next until the target is found, or all items are scrutinised.

The development of visual search across the lifespan has been extensively investigated (Hommel et al., 2004a; Plude, Enns, & Brodeur, 1994; Trick & Enns, 1998). The developmental trajectory for visual search across the entire life span is characterised by a U-shaped trajectory; performance improves gradually through childhood, plateaus at young adulthood and declines during later life. In addition, this pattern of development is more pronounced for serial search tasks compared to parallel search tasks (Hommel, Li, & Li, 2004b); serial search proficiency is more vulnerable to age-related degeneration than parallel search. Studies of visual search development during childhood have shown that search times (Ruskin & Kaye, 1990) and the influence of distractor frequency on search time decrease as a function of age (Trick & Enns, 1998). Interestingly, this trend is more pronounced for serial search than parallel search, with participants producing better performance and shallower set-size slopes for the latter. It is hypothesised (Hommel et al., 2004b) that the pronounced

development of serial search is due to age-related increases in top-down attentional control, while the negligible changes in parallel search originate from bottom-up perceptual performance.

Neuroimaging studies have revealed a large network of brain regions to be involved in visual search. These include the superior parietal lobule, lateral premotor cortex, anterior cingulate gyrus, and the frontal eye fields (FEF) (Mesulam, 1999). The FEF and lateral premotor cortex are involved in exploratory eye movements (Booth et al., 2003) while the anterior cingulate is involved in response monitoring (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999). Comparison of conjunction and feature search has revealed substantially more activation in the superior parietal lobule during conjunction search (Corbetta, Shulman, Miezin, & Petersen, 1995; Coull, Walsh, Frith, & Nobre, 2003). This suggests that the superior parietal lobule has a greater role in serial search than parallel search (Ashbridge, Walsh, & Cowey, 1997; Walsh, Ellison, Ashbridge, & Cowey, 1999). Other cortical areas important in visual search are prefrontal regions and the basal ganglia, which relate to response inhibition (Casey, Durston, & Fossella, 2001).

Several developmental disorders are known to exhibit variations of attention deficits or present with abnormal visual search behaviours (Brenner et al., 2007; Kemner, van der Geest, Verbaten, & van Engeland, 2004; Scerif et al., 2005). For instance, autistic individuals exhibit unusual fixation trajectories when observing complex social scenes (Klin, Jones, Schultz, Volkmar, & Cohen, 2002), and young autistic children and toddlers display an elevated number of saccades during visual search tasks (Kaldy, Kraper, Carter, & Blaser, 2011; Kemner et al., 2004). In contrast, Williams and Fragile-X syndrome children present typical saccadic eye movement during visual search but produced a larger number of errors compared with typically developing children (Scerif et al., 2005).

2.3.2 Language

Understanding how children with IMDs acquire new words, both in terms of comprehension and production is explored in the current body of work. Specifically, we'll investigate the existing size of the children's vocabulary, for production and comprehension, as well as the rate at which individuals can acquire new words. In order to acquire new words, it is vital to segment them from utterances and store enough semantic, syntactic, nonverbal, and phonological information to retrieve them consistently over time (Gathercole, 1999; Gray, 2006). In part, this function relies upon phonological working memory mechanisms - the individual must process and store the order and identity of phonemes within an utterance to accurately recall the new word or to successfully transfer the new word on to long-term memory (Baddeley, 2003; Gathercole, 1999). Consequently, difficulties at either the storage or retrieval phase may lead to problems in new word learning (Gray & Brinkley, 2011; Gray, 2006). One other mechanism involved in word acquisition is "fast mapping" (Carey, 1978) which enables children to immediately and accurately "map" a phonological form to the corresponding semantic meaning (Gray, 2006; Kan & Kohnert, 2008). It has been hypothesised that this ability is a significant contributor to the rapid vocabulary expansion which occurs at about 18 months of age (Heibeck & Markman, 1987). In addition, following the initial exposure to a new word a process called "slow-mapping" (Carey, 1978) can occur, whereby the existing phonological, lexical, and semantic representation of a word can be strengthened through repeated exposures. The proficiency of fast- and slow-mapping increases as a function of age and existing vocabulary knowledge (Alt, Plante, & Creusere, 2004; Chiat, 2006; Gray, 2006; Storkel & Adlof, 2009; Storkel, 2003).

A significant proportion of the patients included in the current thesis have a bilingual background. As mentioned above, successful fast-mapping is influenced by both age and

existing vocabulary knowledge. Hence, research has suggested that bilingualism can reduce the success rate of fast-mapping for second language words, potentially delaying English vocabulary proficiency during childhood (Kan & Kohnert, 2008; Leseman, 2000; Uccelli & Paez, 2007). In a typical word learning task participants are exposed to several novel objects / characters and are required to learn the names of the respective referents (Alt et al., 2004; Gray & Brinkley, 2011; Gray, 2004; Kan & Kohnert, 2008). The speed of learning is partially dependent on the accuracy with which words are mapped to the referent during the first exposure (fast-mapping) and particially on the following number of exposures required to consistently reproduce a referent's name over time (slow-mapping). During the task, a single exposure will involve introducing the child to a set of novel words (e.g. 'yurk') and corresponding referents (e.g. a novel figure). The child then receives an expressive or receptive probe and is required to name or point to the correct novel referent respectively.

The disruption of fast-mapping proficiency has been widely reported in children with specific language impairment (SLI)(Gray & Brinkley, 2011; Gray, 2004; Rice, Buhr, & Oetting, 1992; Rice, Oetting, Marquis, Bode, & Pae, 1994), which is believed to be due to problems creating and storing semantic representations of new words (Alt et al., 2004; Gathercole, 1999). When compared to healthy developing children, children with SLI require a greater number of exposures to successful map referents to novel targets.

2.3.3 Oculomotor Function

Eye tracking tasks provide a non-invasive and objective insight into the neurophysiological underpinnings of disease. Therefore, they are appealing as early stage biomarkers of neurodegenerative disease (Anderson & MacAskill, 2013). In broad terms there are two classes of eye movements. One class are ballistic movements (saccades) that allow us to bring peripheral targets quickly into foveal focus. The second class of eye movement stabilise foveal vision in relation to the movements of our surroundings through

the employment of fixations, smooth pursuit and vestibular-ocular reflexes. In the current thesis, these oculomotor functions are examined in IMD individuals through the examination of eye movements during fixation, pro-saccade, anti-saccade, and smooth pursuit tasks.

There is a substantial body of research detailing the neural mechanisms which control saccadic eye movements. Typically, saccadic eye movement is assessed using pro- and anti-saccade tasks. Pro-saccade tasks measure the reflexive properties of externally-guided saccades, whereby participants must look towards a peripherally presented target as soon as it appears. Common measures for this paradigm include the time in which a reflexive saccade is initiated after the target onset, saccade velocity, and the spatial accuracy of saccades. Anti-saccade tasks follows a similar paradigm, however the moment the peripheral object appears the individual must suppress a reflexive saccade and instead produce a voluntary saccade in the direction opposite the visual stimulus. Here the individual must inhibit the automatic and peremptory response of looking towards the visual stimulus, a behaviour which encompasses several executive functions: response inhibition, response preparation, working memory (Klein, Raschke, & Brandenbusch, 2003; Klein, 2001). Age-related change has been observed in both pro- and anti-saccade tasks (Fischer & Weber, 2010; Klein & Foerster, 2001; Klein et al., 2003; Klein, 2001; Luna, Velanova, & Geier, 2008; Munoz & Everling, 2004; Salman et al., 2006). In general, the reaction time of pro-saccades decrease gradually until around adolescence, while anti-saccade reaction time and error rate exhibit far steeper improvements during this stage of development.

Smooth pursuit is defined as the ability to track small, slow moving objects by maintaining the dynamic object within foveal vision (Fukushima, 2003). This behaviour is achieved by employing non-ballistic eye movements that match target velocity to gaze velocity. A typical paradigm will require the participant to follow a small stimulus that travels horizontally or vertically along a sinusoidal path across the visual field. In these tasks

performance can be measured as “gain” (the mean target velocity divided by mean eye velocity), which indicates how accurately the individual can match eye-to-target velocity. One other measure is the frequency of saccades during tracking and, in particular, the number of catch-up saccades that are executed (Hutton & Kennard, 1998; Ross, Hommer, Radant, Roath, & Freedman, 1996). A catch-up saccade occurs when the individual is unable to maintain accurate gaze velocity matchted to target velocity which leads to gaze falling behind the target. In response, the individual employs a ballistic eye movement in order to re-establish gaze to target velocity. A high frequency of catch-up saccades indicates an impairment of the pursuit system and the saccadic system is being recruited to compensate.

An important element of eye movements is that different oculomotor functions (pro-saccadic eye movement, anti-saccadic eye movement, and smooth pursuit) have distinct neurobiological bases (Karatekin, 2007). Saccades are generated by the six extra-ocular muscles (Demer, 2004) through innervation from oculomotor, trochlear and abducens motor neurons, which receive burst signals from premotor burst neurons in the brainstem. Horizontal and vertical saccades are generated by independent extraocular muscles, motor and premotor neurons (Horn, Buttner-Ennever, Suzuki, & Henn, 1995). For example, horizontal extra-ocular muscles receive input from motor neurons in the abducens nucleus which receive saccadic commands from the paramedian pontine reticular formation (PPRF). Vertical extra-ocular muscles are innervated by motorneurons in the oculomotor nucleus, which receive saccadic signals from burst neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). The discharge rate of premotor neurons is proportionate to the size of the executed saccade (Leigh & Kennard, 2004). During times of fixation, premotor neurons are inactive due to inhibitory signals received from omnipause neurons in the pontine nucleus raphe interpositus (Horn, Büttner-Ennever, Wahle, & Reichenberger, 1994). Another important brain region involved in saccade production is the

cerebellum. The primary role of the cerebellum is to determine the time when saccades need to stop in order to accurately land on a visual target (Noda & Fujikado, 1987).

The neurons in the brainstem and cerebellum are responsible for the temporal properties of saccades (size, start and stop time). Evidence from fMRI and TMS studies has highlighted the role of several cortical and subcortical regions that interact with the superior colliculus (SC) to program the spatial properties of saccades. It is suggested that the SC is responsible for the spatial-temporal transformation of saccadic information (Leigh & Kennard, 2004). The SC receives topological spatial information representing the direction and distance of visual stimuli from the frontal (FEF), parietal (PEF) and supplementary eye fields (SEF), and the dorsal lateral prefrontal cortex (DLPC). From these areas, the SC acquires both direct excitatory input and indirect inhibitory input via basal ganglia (specifically substantia nigra par recticulata and caudate nucleus). The SC encodes this spatial information on a 'motor map' in polar coordinates; activation of rostral and caudal areas elicits smaller and larger saccades respectively. Stimulation of the rostral pole suppresses saccades through the transmission of excitatory signals to omnipause neurons, thus maintaining fixation (D P Munoz & Wurtz, 1992). The caudal distance of collicular neuron stimulation from the rostral pole is relative to the magnitude of gaze displacement (Bergeron & Guitton, 2001; D P Munoz & Wurtz, 1992).

Distinct cortical regions are involved in the function of specific oculomotor behaviours. The input from the PEF to the SC has been shown to be important in triggering reflexive visually guided saccades (pro-saccades) (Shadlen & Newsome, 2001; Wurtz, Sommer, Paré, & Ferraina, 2001), while frontal regions, the FEF and DLPC, have been shown to be important in the suppression of reflexive saccades and production of voluntary saccades (anti-saccades)(Connolly, Goodale, Menon, & Munoz, 2002; DeSouza, Menon, & Everling, 2003; Mort et al., 2003). The DLPC has also been linked to the maintenance of

fixations by inhibiting saccade neurons in the SC and FEF (Tinsley & Everling, 2002). Smooth pursuit eye movements utilise many of the cortical regions involved in saccade generation and several regions exclusive to pursuit (Fukushima, 2003). For example, the caudal area of the FEF is suggested to employ an eye velocity feedback function through the incorporation of target velocity signals from the vestibular and cerebellar systems (Robinson & Fuchs, 2001). This feedback loop enables the accurate prediction of target velocity in order to maintain the target within the retinal image of the foveae.

The neurobiological basis of eye movements has been extensively studied, therefore eye movements are potentially valuable biomarkers for several neurodegenerative and developmental disorders. For example, Niemann-Pick C disease (a lysosomal storage disorder) causes the degeneration of midbrain premotor neurons (Rottach et al., 1997), which leads to progressive vertical saccade slowing and preserved horizontal saccade velocity. Degeneration of cortical and subcortical areas has been shown to affect eye movements in Parkinson's disease (PD), frontotemporal dementia (FTD) and Alzheimer's disease (AD). In PD, the over-activity of the basal ganglia (specifically the substantia nigra), which sends inhibitory output to the superior colliculus, has been linked to the production of hypometric saccades early in the disease course (Liu & Basso, 2008). Prolonged latencies of voluntary saccades are also characteristic in PD (Bronstein & Kennard, 1985; Crawford, Goodrich, Henderson, & Kennard, 1989), whereby the extent of latency increase correlates with disease severity. These latter features are believed to represent wider cognitive degeneration associated with the spread of non-dopaminergic neural dysfunction rather than over-activity within the substantia nigra (T. J. Anderson & MacAskill, 2013). For dementias, oculomotor behaviours are compromised depending on the region of neurodegeneration. For example, AD patients that possess degeneration of the parietal and frontal lobes will exhibit prolonged reflexive saccade initiation and reduced saccade suppression respectively (Garbutt et al.,

2008). In contrast, FTD patients, who are spared parietal degeneration, only exhibit reduced saccade suppression (Currie, Ramsden, McArthur, & Maruff, 1991).

Finally a robust finding within the schizophrenia literature is that schizophrenic individuals possess an impaired smooth-pursuit system (Broerse, Crawford, & den Boer, 2001; Hutton & Kennard, 1998; Karatekin, 2007; Reuther & Kathmann, 2004; Trillenberg, Lencer, & Heide, 2004). Studies have consistently demonstrated that schizophrenic individuals exhibit reduced gain during pursuit tasks (Jacobsen et al., 1996; Kumra et al., 2001; Ross et al., 1996; Ross, 2003). Interestingly, these findings are also evident in remitted patients and unaffected relatives of schizophrenic individuals.

3.0 GENERAL METHODS

3.1 Introduction

The following section details the methodology of the tasks used within the test battery. Description of the tasks are organised into sections based on the three cognitive domains – attention, language, and oculomotor function. Task descriptions include the experimental procedure, outcome measures, and the treatment of data prior to analysis. The specific details of how the data were analysed is described in later chapters. For example, the method for analysing healthy developmental trajectories is given in the control results chapter (Chapter 4), while the method used to compare patients to controls is described in the first patient chapter (Chapter 5).

3.2 Attention

Attention was measured with two tasks: a simple reaction time task and a visual search task. The simple reaction time task always preceded the visual search task. This allowed participants to be familiarised with the stimuli (red ladybird) used as the target in the following visual search task.

Apparatus & Procedure

For both tasks, stimuli were created using Experiment Builder (SR Research Ltd., Mississauga, Ontario, Canada). Participants viewed the stimuli from 60 cm away on a 41 x 30 cm (width x height) desktop monitor, producing a search area of 37.73° x 28.07° (width x height) of visual angle for participants to complete the tasks. Stimuli in both tasks consisted of cartoon red ladybirds, green ladybirds and red beetles. Responses were recorded using a Cedrus button box. (http://cedrus.com/).

Simple Reaction Time Task

The task measured the speed of visual target detection. Participant completed 20 trials where a red ladybird (5.73° x 7.64°) was presented in one of four quadrants of the screen against a white background. The size of each quadrant was 10° x 8.8°, and was at a diagonal distance of 11.89° from the screen centre. Across trials the target appeared at each quadrant 5 times, with the order of the target locations being randomised between participants. The participant needed to respond using the a single button on a button box as quickly as possible, with their preferred hand, when the target appeared (Figure 3.2.1).

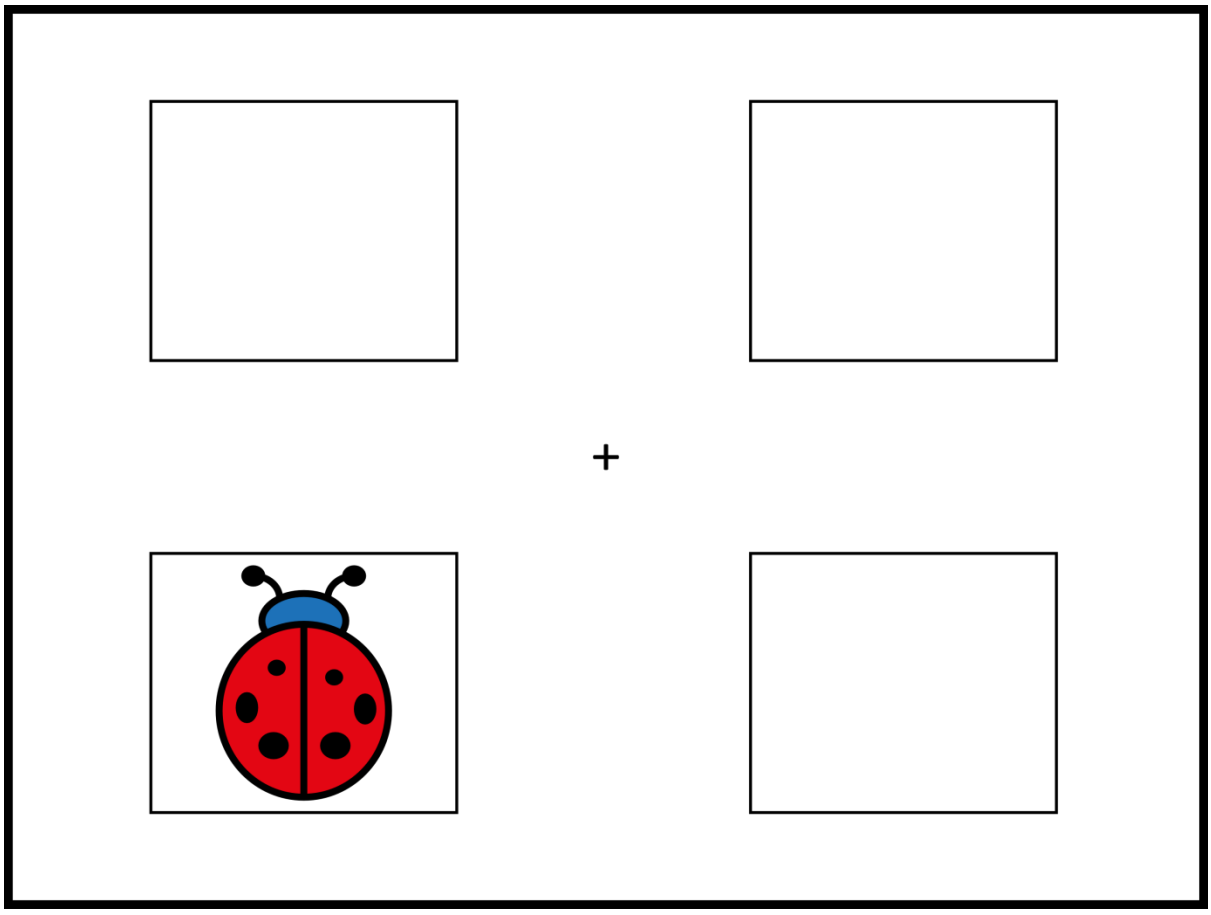


Figure 3.2.1: Example of a simple reaction time trial. Here the visual target is presented in the bottom-left quadrant of the display. Participants are required to respond to the presence of the visual stimulus as soon as it appears.

Trials began with a centrally presented fixation cross (1.15° x 1.15° of visual angle) for 1000ms, which was followed by the appearance of the quadrants. After a variable delay (500 - 3000ms) the red ladybird target stimulus was presented in one of the four quadrants. The stimulus remained on the blank screen until the participant made a response or if 3000ms passed without a response. Following a response a blank screen was presented for 1000ms prior to the presentation of the fixation cross of the following trial.

For the simple reaction time task the time taken to detect and respond to a target, relative to the target's appearance, was measured in milliseconds (ms). Mean (*RTmean*) and standard deviations (*RTstd*) were calculated for the response times of individual target quadrants and for response times collapsed across quadrants.

Visual Search Task

The visual search task consisted of 3 feature search blocks and 3 conjunction search blocks. In both task types participants indicated whether a target character (red ladybird) was present with a "Yes" button, or absent using a "No" button, on a Cedrus button box. During feature search trials (Figure 3.2.2, panel A) the participant was required to search for the red ladybird among a set of green ladybird distracters (Stimuli size = 3.80° x 5° of visual angle). For the conjunction search trials (Figure 3.2.2, panel B) participants needed to search for the red ladybird among green ladybirds and red beetle distractors. Each block contained 12 feature or conjunction search trials (a total of 36 feature search trials and 36 conjunction search trials) with 3 set sizes (4, 8, and 12 items). The target was present in half the trials of each block, and absent in the other half. Block order was randomised between participants.

A total of 16 locations were created by dividing the screen into a 4x4 grid, with each grid location having a size of 9.80° x 7.35° of visual angle. For each trial the target and distractors had a possibility of randomly appearing in any of the 16 grid locations. The stimuli items were presented at the centre of the grid location. In order to make target and distractor displays appear more natural, each item's x and y axis position was jittered between ±1.9° and ±0.95° of visual angle respectively. During feature search blocks, all stimuli items of the target-absent trials were green ladybirds; for target-present trials the target stimulus replaced one of the distractor items. For conjunction search blocks, half the items were red beetles and half were green ladybirds during target-absent trials; for target-present trials a red beetle distractor was replaced with the target red ladybird to ensure the number of red and green elements were equal.

The Visual Search Task began with 4 practice trials in order to familiarise participants with the task. During these practice trials feedback was provided on screen ("correct" or "incorrect", presented centrally) to the participants. Following the practice trials, the participant began the first block of the task. Each trial began with a centrally presented fixation cross for 1000ms that was followed by the stimulus presentation. When the stimulus appeared the participant used a Cedrus button box to make a response; press the left button if target is present or the right button if target is absent. The stimuli presentation disappeared upon the participant's response or if no response was registered within 10 seconds. A blank screen was displayed for 1000ms prior to the following trial. At the beginning of each block participants were presented with a screen that informed them of the type of upcoming search task, feature or conjunction. This was achieved by displaying which items would be shown (feature: 'red ladybird' and 'green ladybird', or conjunction: 'red ladybird', 'green lady bird' and 'red beetle') and from verbal instruction given by the experimenter.

Two measures were taken for the feature and conjunction conditions: mean response time (*VSmean*) of correct responses measured in milliseconds (ms) and set-size search efficiency (*VSslope*). Latency was calculated as the time taken to respond correctly from stimulus presentation onset. Search efficiency represented the time that participants required to scrutinise each additional item in the search display. Search efficiency was calculated as the change in mean responses as a function of the set size conditions (4, 8, and 12 items).

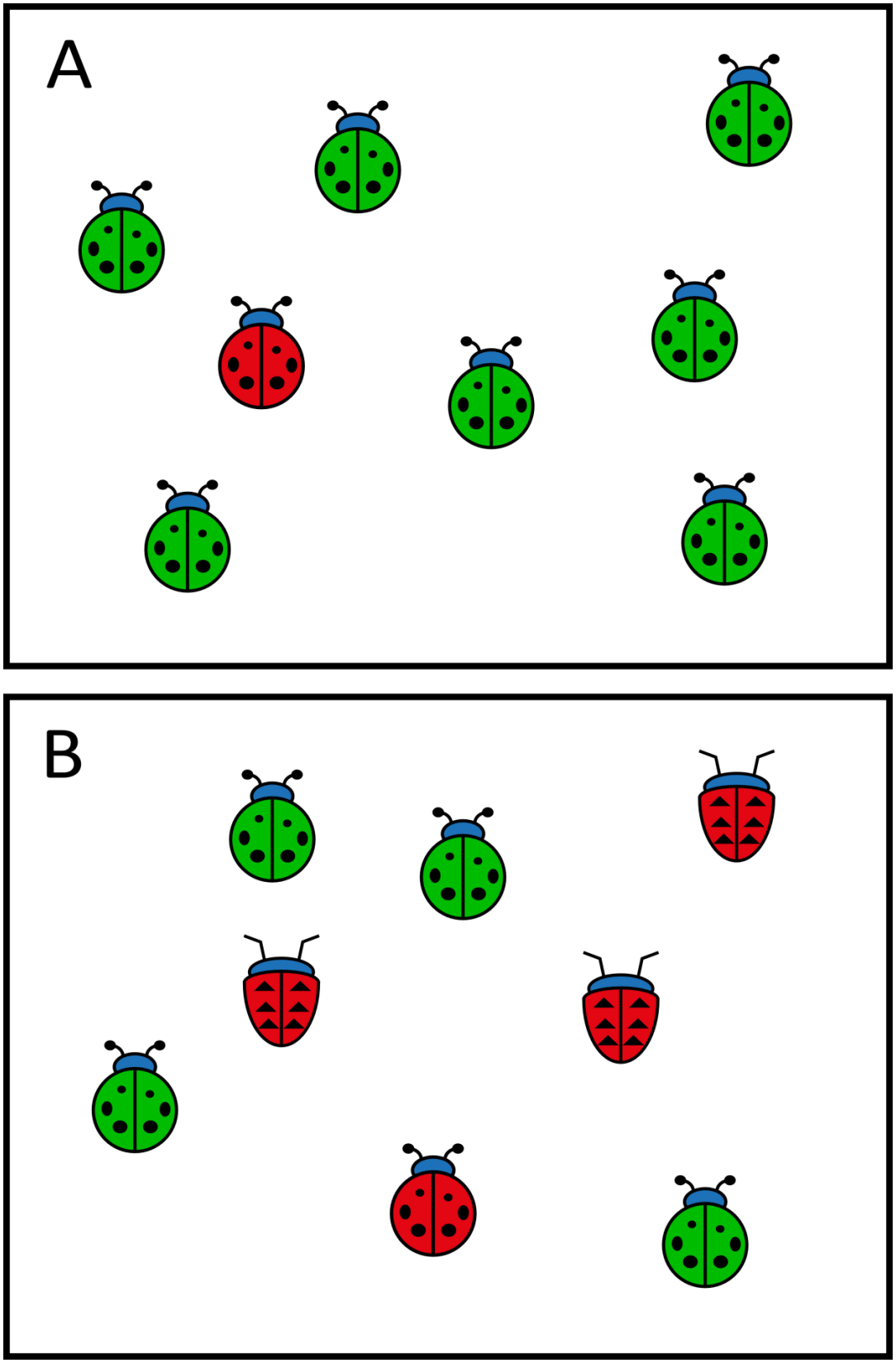


Figure 3.2.2: Visual search trial example. Feature and conjunction search shown in panel A and B respectively. In both examples the target (red ladybird) is present.

3.3 Language

Three tasks were used to assess children's language function, i.e. the Boston Naming Task (BNT; Kaplan, 2000), the British Picture Vocabulary Scale (BPVS; Dunn et al., 1997) and a novel non-word learning task.

Boston Naming Task (BNT)

The BNT is a measure of picture-naming and has been frequently used in various clinical settings; such as the evaluation of patients with acquired brain damage and the effects of progressive dementia in Alzheimer's disease (Mack, Freed, Williams, & Henderson, 1992; Neils et al., 1995). It has also been successfully utilised in the examination of individual differences produced by bilingualism (Kohnert, Hernandez, & Bates, 1998) and educational background (Neils et al., 1995). The BNT is a 60-item task where the examiner sequentially presents pictures to the participant which increase in difficulty (high- to low- frequency words). Participants will be initially presented with high-frequency items ("bed") and will be presented with low-frequency items ("abacus") if they are able to successfully progress through the test. Cues are offered if the participant cannot find the item's name. The first cue offered is always semantic and a phonetic cue is offered if a semantic cue does not produce a correct response. For the item "bed", the semantic cue was "It's a piece of furniture" and the phonetic cue was "It begins with the sounds 'Bi'". An item was scored as correct if the participant was able to produce the name with or without a semantic cue, and incorrect if the participant failed to produce the item name or if production was only possible with a phonetic cue. The task was terminated if the participant made more than 5 consecutive errors or if all 60 items were completed.

British Picture Vocabulary Scale (BPVS)

The BPVS is a measure of receptive vocabulary that is typically used with children aged 3-15 years. It is a popular language measure since vocabulary is considered to be a sensitive measure for a wide range of language skills. The test was administered from a test book where each page presents the child with four black and white line drawings. For each page the experimenter verbally presents the child with a name and the child is asked to match the name to the correct picture (by pointing to it) from the set of 4 pictures. This is important as it does not require an articulated response; hence, vocabulary can be assessed for children who possess speech production deficits. There are 14 sets of 12 items, resulting in 168 stimuli in total, with the complexity of word sets increasing as the child progresses through the sets. The test terminates once the child makes eight or more errors on a single set. The child's test score is based upon the total number of words that are correctly identified. BPVS raw scores will be used in the analysis to draw comparisons between patients and controls.

Non-Word Learning Task

The non-word learning task required participants to identify and verbally produce the names of non-words that had not been previously learned. All non-words were 2-syllable words that respected the phonotactic constraints of the English language. Children learned the non-words as names for a set of 5 cartoon monsters that were each presented on 15 x 21cm cards (width x height; Appendix 1). The task was administered in 2 stages: a learning and delayed recall stage. Prior to stage 1, children were asked to repeat the names 3 times to ensure name production was possible.

In the first stage, learning was measured during 6 learning iterations. Each learning iteration consisted of 3 phases. Phase 1 was the model phase – the 5 monsters were sequentially modelled by the experimenter ("This is [Monster Name]. Can you say that?") and participants were required to repeat the names as they were given. Phase 2 was the comprehension phase – the experimenter administered a comprehension probe ("Can you point to [Monster Name]") for each monster, the participant was required to point to the correct monster. Phase 3 was the production phase – the experimenter administered a production probe ('What is this monster's name") for each monster, the participant was required to produce the name of the relevant monster. During the two probe phases, participants received 1 point for each correct probe response and were given feedback about the accuracy of responses. For production only, participants received half a point if they were able to accurately produce one the first syllables of a monster's name. The order that monsters were modelled and probed was randomised between the iterations. The sum of points acquired over the course of the 6 learning iterations (total: 30 points for production and 30 points for comprehension) was taken as the measure of non-word learning.

3.4 Oculomotor function

We investigated oculomotor function using four established oculomotor paradigms within developmental and atypical developmental research – a fixation task (Gould, Bastain, Israel, Hommer, & Castellanos, 2001; Klockgether, Petersen, Grodd, & Dichgans, 1991), a pro- and anti-saccade task (Fischer & Weber, 2010; Christoph Klein, 2001; Douglas P Munoz & Everling, 2004; Salman et al., 2006) and a smooth-pursuit task (Katsanis, Iacono, & Harris, 1998; Tregellas et al., 2004). The inclusion of these tasks enabled the assessment of distinct components of the oculomotor system; specifically the saccadic eye movement system and

smooth-pursuit system. Therefore, we were able to observe whether impairments of the ocular motor system affected only specific mechanisms (i.e. saccadic eye movements) or whether mechanisms were globally impaired. The methodology of the four ocular motor tasks is described in the following section.

Apparatus

For all ocular motor tasks, participants were seated 60cm away from a 32 × 26cm CRT-monitor with dimensions of 1024 by 768 pixels and a refresh rate of 60 Hz . Eye movements were recorded via eye-tracking equipment (EyeLink® 1000 Tower Mount Head Supported System; SR Research Ltd., Ontario, Canada). The equipment provides information on the location and duration of fixations by measuring corneal reflection via an infrared camera. Participant head movements were stabilized with forehead and chin rests. All stimuli were created using programming software (SR Research Experiment Builder, version 1.10.165) suitable for conducting eye-tracking experiments. Eye movements were recorded at 1000 Hz with the tower setup. Eye movements were calibrated to an accuracy of at least 1° using a nine-point calibration array. Drift correction was employed on each task at the beginning of each trial in order to assess the quality of calibration. Participants could be recalibrated if excessive head movements disrupted calibration.

Procedure

Fixation Task

In the fixation task, participants completed 20 trials where they maintained fixation on an elephant face target (1.5° in size) which could appear in one of four randomly selected locations around the screen centre (Figure 3.4.1).

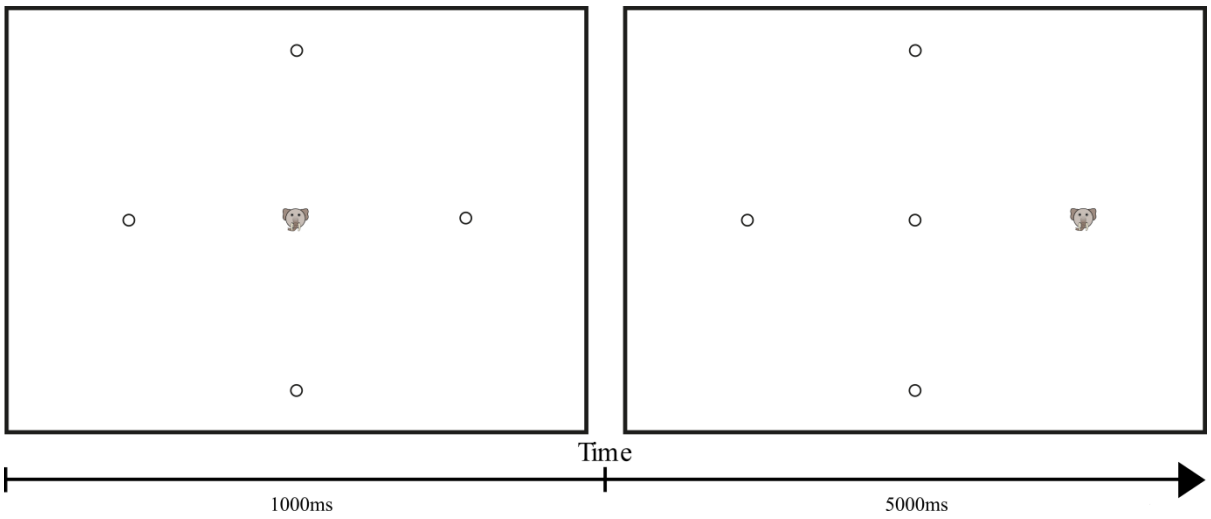


Figure 3.4.1: Fixation task trial example. Participants are initially presented the target centrally for 1000ms. The target then disappears and immediately reappears at one of the four surrounding locations for 5000ms.

The possible target locations were marked with small circle markers (0.5° in size) to indicate the locations the target could appear. These locations were positioned immediately above, below or to the left or right of a central fixation point at an eccentricity of 8°. Prior to the beginning of each trial, the quality of calibration was checked using a drift correction. Trails began with the presentation of the target centrally for 1000 milliseconds (ms). After 1000ms, the target would disappear and immediately reappear (no gap or overlap) at one of the four surrounding locations. The target would remain at this location for 5000ms. At the end of the 5000ms, the stimulus was removed and the participant was presented with a blank white screen for 1000ms.

Saccade Task (Pro- and Anti-Saccade)

Two tasks were employed to investigate the saccadic eye movement of the patients: a pro-saccade and an anti-saccade task. In both tasks, participants viewed 48 trials where a target elephant face (1.5° in size) randomly appeared at one of eight locations around a central

starting position. The same four locations were used from the fixation task (see above), with four additional locations positioned above, below or to the left or right of the screen centre at an eccentricity of 4°. Each trial began with the stimulus appearing at the centre of the screen for a random amount of time between 1000 and 2000ms. The stimulus then disappeared and reappeared at one of the possible target locations for 1000ms (Figure 3.4.2) without any gap or overlap.

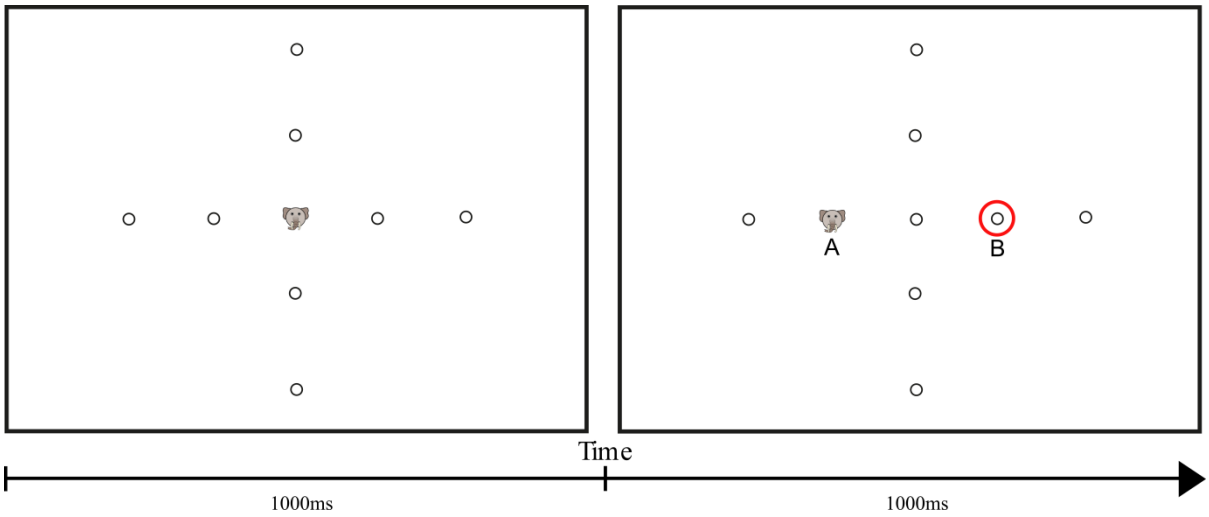


Figure 3.4.2: Pro- and Anti-saccade task trial example. Participants are initially presented the target centrally for 1000ms. After the target reappears, the participant has 1000ms to execute an eye movement towards location A or B for the pro- and anti-saccade task respectively.

During the pro-saccade task, participants were asked to look as quickly and accurately as possible at the target after it moved to one of the target locations. For the anti-saccade task, participants were required to inhibit the production of a reflexive pro-saccade towards the stimulus after it moved. Instead, participants needed to produce a voluntarily eye movement to the mirror opposite location from the stimulus. For example, if the stimulus appeared 8° to the right of the centre, the participant needed to look to the position 8° to the left.

Smooth Pursuit Task

For the smooth pursuit task participants were instructed to maintain fixation for 10 seconds on a moving target stimulus (1.5° in size) on 3 separate movement trajectories - horizontal movement, vertical movement, and elliptical movement. Each movement trajectory was presented at slow and fast velocities, resulting in 6 distinct trajectory and velocity combinations. Participants completed 24 trials, organised into 6 blocks (4 trials per block), where each block consisted of trials of a single trajectory and velocity combination. The order of blocks was randomised across participants.

For horizontal and vertical trajectories, the target moved left/right and up/down, respectively, along a 16° path positioned in the middle of the screen. The target moved at two sinusoidal velocities of 0.2 and 0.5 Hz, equating to an average target velocity of 6.5° and 16° of visual angle per second respectively. For vertical trajectory trials, trials always began with the target presented at the centre of the screen. Sinusoidal movement of the target would commence along an upward trajectory on slow velocity trials, and a downwards trajectory during fast velocity trials. On horizontal trials, the starting position of the target depended upon the target's velocity. The target's starting position was at the limit of the sinusoidal trajectory, either 8° to the left or right of the screen centre for slow and fast velocities respectively.

For the elliptical trajectories, the target moved around the centre of the screen at a constant eccentricity of 8°. The target moved at two constant velocities; either at 0.2 or 0.3 Hz over 10 seconds, which averaged at 10° and 15° of visual angle per second respectively. For both trajectory velocities the position of the target at the beginning of each trial was 8° to the left of the screen centre. From this starting position the target moved in a clockwise or an anti-clockwise direction, for slow and fast velocities respectively.

Measures

For the fixation and saccade tasks eye position data were transferred to a computer (Eyelink 1000, SR Research) in real time to determine saccade detection and fixation location. The onset of a saccade was detected if the velocity of an eye movement velocity exceeded 22°/second and eye position changed more than 0.3°. Saccade amplitude was defined as the difference between eye position at the onset and offset of a detected saccade. Both velocity and amplitude differences were based on instantaneous calculations of the previous 19 samples. Prior to analysis, trials from all tasks were visually inspected to ensure that participants were engaged in the task and to remove artefacts.

Fixation Task

For the Fixation task we measured participant's ability to maintain fixation by observing target fixation duration (*FixDwell*) and target engagement (*FixSacc*). For each target, a surrounding 2.8 x 2.8° box classified the target's respective region of interests (ROI). Fixations that fell within these ROIs counted as fixations on a target. *FixDwell* was defined as the length of time that participants maintained eye position within the target's ROI once it appeared. *FixSacc* was measured as the frequency of saccades (greater than 2°) that moved the participant's gaze outside the target ROI, and was intended to indicate deviation of attention.

Pro-saccade Task

For the pro-saccade task we investigated the basic operation of patients' reflexive ocular motor function. Saccades were required to meet several criteria in order to be classified as a pro-saccade. First, at onset, the saccade must have been positioned at the centre of the screen, at the location of the stimulus prior to moving. Secondly, the direction of the

saccade needed to be made in the direction of the peripheral stimulus location. For saccades that met the inclusion criteria, we measured the saccadic reaction time (*SaccOnset*) of the first eye movement executed towards the peripherally presented target location. In addition, the velocity of eye movements was quantified by peak velocity (*SaccVelocity*); the peak of velocity during an eye movement.

Anti-saccade Task

For the anti-saccade task we investigated participants' ability to inhibit reflexive eye movements towards peripherally presented cues, instructing them to instead to fixate on a position situated directly opposite the cue – i.e. produce an anti-saccade. We quantified this behaviour using several measures: the offset of the saccade which brings the participants gaze to the anti-saccade target (*AntiOffset*), the proportion of trials where a pro-saccade error was produced (*AntiErr*), and the proportion of errors that were corrected (*AntiCorr*).

Saccades were qualified as anti-saccades if the following criteria were met: 1) the position of the saccade at onset was located at the screen centre; 2) the saccade was the first saccade during the trial; 3) the saccade latency was greater than 135ms; 4) the direction of the saccades was made in the direction opposite to the peripheral stimulus cue. A saccade was classified as a anti-saccade error (*AntiErr*) if it followed the same criteria as a pro-saccade from the pro-saccade task and occurred before an anti-saccade. The proportion of trials where errors occurred reflected the failure to inhibit reflective saccades towards a peripheral cue. Error correction (*AntiCorr*) was expressed as the proportion of trials where an error was corrected. Errors were classified as corrected if the saccade following an anti-saccade error was produced in the direction of the anti-saccade target and had a larger amplitude than the preceding pro-saccade error. Latency of anti-saccade target fixation (*AntiOffset*) was measured as the time taken for the participant to locate the anti-saccade location.

Smooth Pursuit

Smooth pursuit analysis was accomplished by manually extracting the sampling data of each trial. This resulted in 10,000 available samples that were first prepared using a computer program, written in R, to extrapolate separate target and eye information for velocity, positional coordinates, and saccade frequency. In order to compare smooth pursuit across the 3 movement trajectory conditions we only included eye movement data that was recorded whilst the target was moving at a constant velocity. Therefore, for horizontal and vertical trajectories, we excluded all samples that were recorded whilst the target was positioned within a 1.5˚region at either end of the trajectory (the tails of the sinusoidal movement). In addition, samples that were classified as blinks or saccades were removed from the smooth pursuit analysis.

Smooth pursuit performance was measured by velocity gain (*VeloGain*) and frequency of catch-up saccades (*ForwSacc*). For each of these variables we explored the effect of the 3 movement trajectories (horizontal, vertical, and elliptical) and the 2 movement velocities (slow and fast). Velocity gain was defined as the average eye velocity divided by the average target velocity. Higher velocity gain scores equated to a closer match between the target and eye velocity, thus the target is likely to be maintained in foveal vision. Catch-up saccades were eye movements where the velocity was more than 5 SD from the mean eye velocity based on the SD of the velocity in the smoothly moving part of the trial.These were expressed as the average number of catch-up saccades per second on each trial. A higher number of catch-up saccades may indicate problems in the pursuit system and therefore the saccade system is relied upon to minimise distance between the target and eye.

4.0 HEALTHY DEVELOPING CONTROL RESULTS

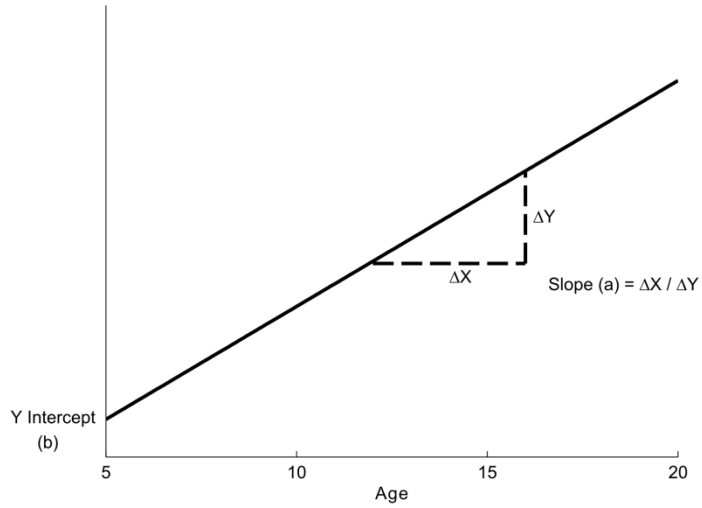
4.1 Introduction

Detecting cognitive impairments, whether global or domain specific, is a challenge when investigating rare and neurologically complex populations (Martin et al., 2008). Firstly, due to the rarity and geographical dispersed nature of individual inherited metabolic disorders (IMDs), neuropsychological research within this area has been extremely limited. A small range of studies exist examining the cognitive function of metabolic disorders (Bendadi et al., 2014a; Davison et al., 2012; Shapiro et al., 2009), but due to their limited sample sizes finding robust statistical support has been challenging. Secondly, the heterogeneous onset and severity of neuropsychological features associated with IMDs further complicate the identification of cognitive developmental features and trajectories within these populations. Together with the advent of many promising treatments, such as enzyme replacement therapy and haematopoietic stem cell transplantation, it is vital that a sensitive method of quantifying the neurodegenerative effects of these disorders is established.

Identifying the presence of cognitive impairment in the current thesis, whether global or domain-specific, is achieved through two means: The direct comparison of individual patients to a large group of healthy developing controls, and the comparison of developmental trajectories between patients and healthy developing controls. To this end, tasks in the test battery have been standardised with a large sample of healthy developing controls in order to identify which tasks are most sensitive to developmental effects, to establish development trajectories for each task, and provide a means to compare patient performance. In this section we analyse results from healthy controls to determine which developmental trajectory model is appropriate for each of the measures outlined in Chapter 3.

4.2 Data Analysis – Developmental Trajectories

We compare models for developmental trajectories (ages 5-19) using Akaike's Information Criterion (AIC) as a model selection paradigm. We fit three functions to the data: linear, quadratic, and plateau. Figure 4.2.1 outlines each model fit and the related parameters. These three models were chosen since they can each provide unique fits that can explain different patterns in cognitive development. Quadratic and plateau functions (both nonlinear) typically fit developmental data taken from a wide range of ages more accurately than linear functions, as the rate of cognitive change for many tasks is not constant. Early gains are faster and later progress shows slow gains or no change with age. For some of the tasks, children may reach developmental maturation early on within the age range of the sample. In these cases a plateau will fit the developmental data more accurately than a quadratic function since they include an age range where performance changes very slowly or does not change at all with time (and there is no age-related decline in the range we are testing). To statistically answer the question "which function provides the best representation of the developmental data?" we inspected the Akaike's Information Criterion (AIC) values for different functions. In addition, these methods were extended to inspect differences between experimental conditions within tasks to determine the necessity of condition-specific trajectories during healthy cognitive development.



Linear Model

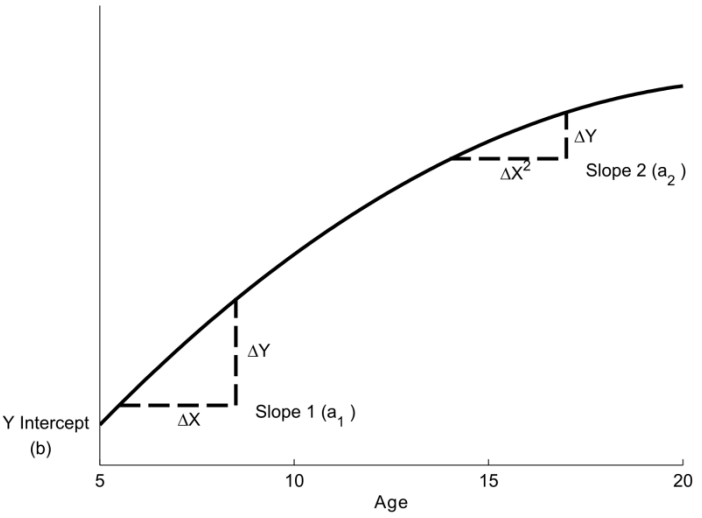
Model

$Y = b + Age * a$

Parameters

Intercept (*b)*: the value of Y at the youngest age of measurement

Slope (*a)*: The rate of development as a function of age.



Quadratic Model

Model

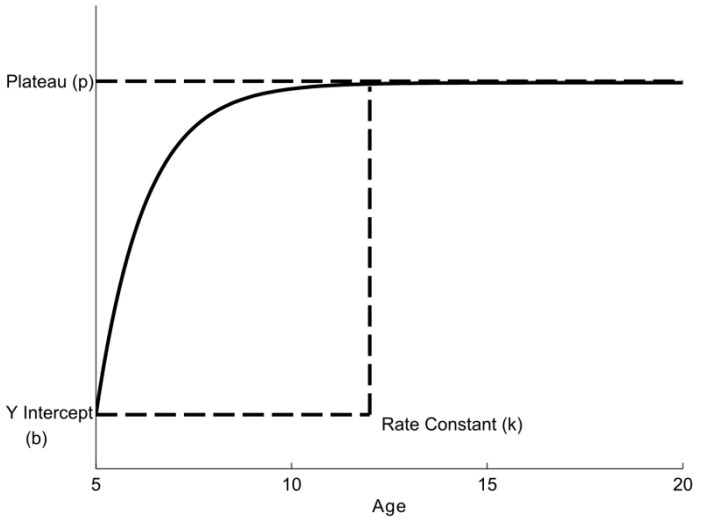
$Y = b + Age* a_1 + Age^2 * a_2$

Parameters

Intercept (*b)*: The value of Y at the youngest age of measurement

Linear Term (a_1): The steepness of development as a function of age.

Quadratic Term (a_2): The direction and gradient of slope bend as a function of age.



Plateau Model

Model

$Y = b + (p - b) * (\exp(-k * Age))$

Parameters

Intercept (*b*): The value of Y at the youngest age of measurement

Plateau (*p*): The value of Y when Age is expressed as an infinite – value of Y at the age of cognitive maturation.

Rate Constant (*k*): The magnitude of development between intercept and plateau

Figure 4.2.1: Description of fitted models and parameters. The 3 fitted models and related parameters of the 3 functions fitted to the developmental data during the model selection stages.

Akaike's Information Criterion (AIC)

Using AIC for model selection is a statistical method grounded in information theory that "allows the data-based selection of a 'best' model and a ranking and weighting of any remaining models from a pre-defined set" (Burnham & Anderson, 2002). AIC can be used as an alternative to likelihood ratio test model comparisons (using *F*-values and based on null-hypothesis testing), as a means to identify whether a model adequately fits a dataset without overfitting the noise that would not be represented in a different sample; If a model is fit with noise in one sample it will not generalise well to a new sample. A good balance between fit and parsimony is what AIC is designed to achieve. Unlike *F*-test model comparisons, AIC can be used to compare both *nested* and *non-nested* models whereas the *F*-test is only suitable for the comparison of *nested* models. This is important since we are interested in comparing both *nested* (e.g. linear and quadratic) and *non-nested* (e.g. linear and plateau) models. Equation 1 is the formula for calculating the AIC statistic of a model. Similar to an *F*-test comparison, the equation utilises the sum-of-squared residuals (SS) created by the model to provide an indication of how well the model minimises the vertical error of data points from the fitted function. In addition, AIC considers the complexity of a model by including the number of parameters (K) fitted by the regression. N is the number of observations. Lastly, in the current work we used corrected AIC values (AIC_C ; Equation 2) which are used for comparing models based on smaller sample sizes (Burnham & Anderson, 2002).

1) $$\mathrm{AIC} = \mathrm{N} \cdot \ln\left(\frac{\mathrm{SS}}{\mathrm{N}}\right) + 2\mathrm{K}$$

2) $$\mathrm{AIC_C} = \mathrm{AIC} + \frac{2\mathrm{K}(\mathrm{K}+1)}{\mathrm{N}-\mathrm{K}-1}$$

The absolute value of AIC is not meaningful. It is the numerical difference between AIC values (without respect to the absolute size) that indicates how far model candidates are from the 'best' model in the set. For the purpose of model comparisons, the first step is to calculate the difference in the AIC values (ΔAIC; Equation 3) produced by a set of models, whereby each model's AIC is compared to the AIC of the 'best' model (model with lowest AIC; AIC_j).

3) $\Delta AIC_i = AIC_i - AIC_{min}$

Consequentially the 'best' model will have an ΔAIC of 0, while the ΔAIC of the remaining model candidates will reveal how close they are to being the 'best' model, thus all models in the set will be ranked. There is not a set method for interpreting ΔAIC values, but rules of thumb exist (Burnham & Anderson, 2002). An ΔAIC of 0-2 indicates nearly equivalent likelihood between the candidate model and the 'best' model, an ΔAIC of 4-7 shows the candidate model has considerably less support, and an ΔAIC > 10 indicates there is virtually no support for the candidate model. Using ΔAIC it is possible to calculate two further useful values - the *AIC weight* (AIC*w*) and then the *Evidence Ratio*. AIC*w* is a relative probability expressing how likely each model is of being the best fit to the data set. Thus the sum of all model AIC*w* within a set will equal 1 (Burnham & Anderson, 2002). It is calculated as follows:

$$AICw_i = \frac{e^{(-1/2\,\Delta AIC_i)}}{\sum_{r=1}^{R} e^{(-1/2 \Delta AIC_r)}}$$

In general, candidate models with large ΔAIC values will produce smaller AIC*w*, and thus present less evidence of being the 'best' model. Below is an example output from a

comparison of the 3 model types (linear, quadratic, and plateau) fitted to a fictitious dataset. The models are ranked in order according of ΔAIC.

Model	AIC value	ΔAIC	AIC*w*	Evidence ratio
Quadratic	100	0	0.95	1
Plateau	107	7	0.03	32
Linear	108	8	0.02	56

In the above example the ΔAIC values show that the quadratic model is preferred (has the lowest AIC value) and, given the model set, has the highest relative probability by some margin (AIC*w* = .95 ; the relative probability of being the best model out of these 3 is 95%). In this example, it would be appropriate to accept the quadratic model as the only appropriate model for the dataset. In a less clear example (below), the likelihood of two models (quadratic and plateau) are nearly equivalent (ΔAIC < 2); While a quadratic model provides the best description of the data, a plateau model also offered a reasonally good fit as well. In this case, it may be appropriate to choose a plateau model over a quadratic model if the fit provided by the plateau model make more developmental sense (i.e. a quadratic model might suggest an unrealistic U-shape developmental curve inorder to achieve a closer stastical fit).

Model	AIC value	ΔAIC	AIC*w*	Evidence ratio
Quadratic	100	0	0.57	1
Plateau	101	1	0.35	1.6
Linear	104	4	0.08	7

A further way of explaining the relative differences between a set of models is to calculate evidence ratios (*Eratio*) for a model set. An evidence ratio can be computed for a candidate model by dividing its AIC*w* by the largest 'best' model AIC*w* from the model set. The ratio expresses how many times more likely the 'best' model is of being correct than the model of interest. For example, in the above example we can see that the quadratic model is 33 (.954 / .029) and 56 times (.954 / .017) more likely to be correct than the plateau and linear models respectively. Together with the AIC*w* values, evidence ratios help to quantify relative differences between models when choosing a "best" model (or models) from a model set.

Using AIC to compare development across experimental conditions

We use model selection with AIC to determine the best way of describing rates of change in development, but also to test for condition-specific trajectories within tasks. For example in the language tasks, does verbal production develop differently to verbal comprehension? To answer these questions we used non-linear mixed effect model analysis (nlme) to compare models that include main effects and interactions. In the context of trajectory comparisons, main effects indicate whether the developmental trajectories of two or more tasks / conditions are offset. Whereas the presence of interactions (which factor in age – *Task* x *Age*) indicate whether the gradient of two or more developmental trajectories differ with age. Figure 4.2.2 provides an example of two possible trajectory comparison outcomes. Panel A shows an example of a main effect without an interaction. The development of the two conditions is offset but the rate of change is the same. Panel B displays an example of a main effect and an interaction. The development is of the two conditions is offset and the rate of development differs.

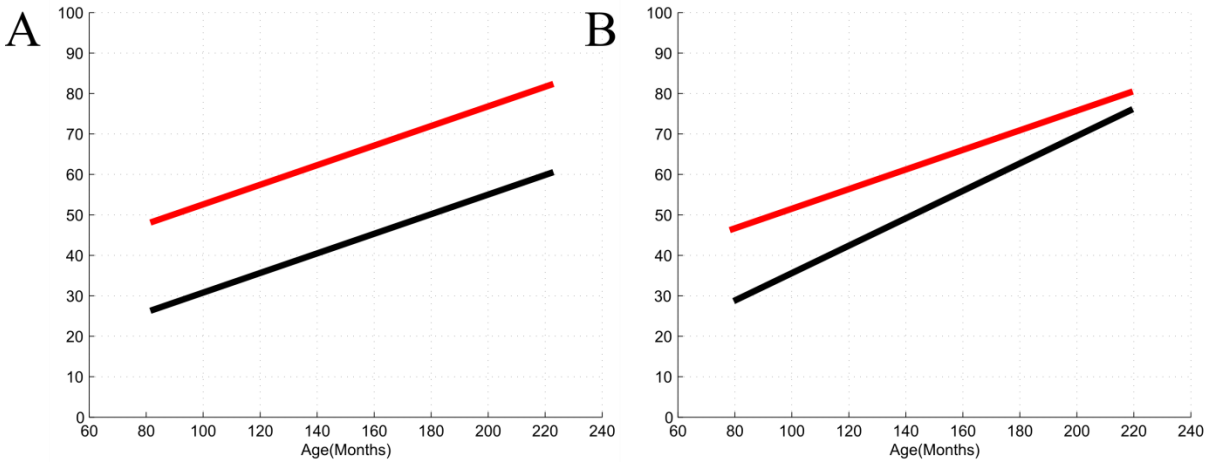


Figure 4.2.2: Trajectory comparison method. Example of main effect and interaction comparison method of two conditions. Panel A illustrates an instance where the development between two tasks is offset, but the rate of development is the same (main effect with no interaction). Panel B illustrates an instance where the development between two tasks is offset and the rate of development differs (main effect and interaction).

For instances where three or more tasks / conditions are compared and main effects and / or interactions are revealed, it is necessary to identify where the differences between trajectories reside. This is achieved through the construction and comparison of model sets, where each model represents particular experimental factor combinations. For example, in the fixation task, 3 separate models could be compared: a 1-term model where a single trajectory defines saccade speed across all target positions, a 2-term model with separate trajectories for up/down and left/right target positions, and a 4-term model that has separate trajectories for all the 4 target positions. In this case, the comparison of AIC values will indicate whether development proceeds uniformly for saccades in all directions, or occurs at a different rate in some directions rather than others.

Definition of Confidence Intervals

Confidence limits for developmental trajectories are defined using a bootstrap method to create 3 comparable function types (linear, quadratic and plateau). These functions are fitted to the 95% interval of the bootstrapped *t*-distributions of the age groups to construct

smooth curves. This method of defining confidence limits is preferable to traditional prediction bands as it minimises the impact of any idiosyncratic variance estimates produced from individual age samples.

The precise method used to define the 95% CIs of the development trajectories is as follows (Figure 4.2.2 provides an illustration). First, the age of participants were rounded to the nearest year to create a set of bins representing different age groups (6 year olds, 8 year olds, 10 year olds, etc.). A new sample is created (random sampling of raw data with replacement; blue dots in Figure 4.2.3, panel A) for each age bin from which upper and lower 95% *t*-based CIs are acquired (red dots in Figure 4.2.3, panel A). Using these CI values a set of 3 functions are fitted (linear, quadratic and plateau) (Figure 4.2.3, panel B). This process was replicated 1000 times (bootstrapped) in order to build a population of parameter estimates for each of the 3 function types. An average was calculated across each population of parameter estimates to produce the best single linear, quadratic and plateau function. The AIC values of these final functions were compared to identify which function best characterised the confidence limits of the developmental trajectory.

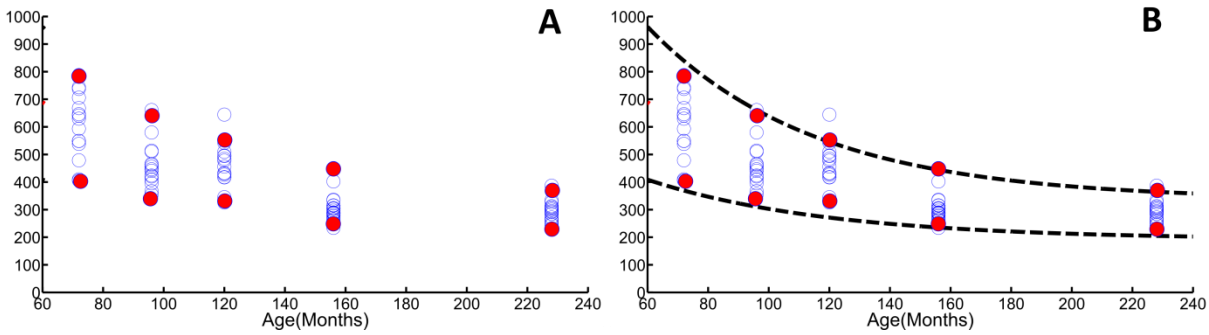


Figure 4.2.3: Process of defining developmental trajectory confidence intervals. In panel A, the upper and lower 95% t-based CIs (red dots) were calculated from a random sample (with replacement) of the data (blue dots) in each age bin. In panel B, 3 regression functions (quadratic is illustrated here) were fitted to the lower and upper points of the 95% CI. This process was replicated 1000 times (bootstrapped) to build a population of fitted curves. Parameter averages were computed from the population of curves to produce a final curve.

4.3 Attention

Participants:

Control data for the attention tasks was collected from a sample of 104 children, teenagers and young adults (age range: 72 – 228 months). Data was collected from primary schools, secondary schools and undergraduate psychology students. Prior to testing, informed consent was taken from undergraduate students or from parents of children who took part from primary or secondary school.

Simple Reaction Time Task

The simple response time latency (*RTmean*) of healthy controls was examined at 4 target locations. In the first step of the analysis, an AIC comparison was conducted to test the 2-way interaction between *TargetLocation* and *Age*. Here a model which included an interaction term (ΔAIC = 0; AIC*w* = .971) was better than a model that did not (ΔAIC = 7 ; AIC*w* = .029). This means the healthy development of simple response time (*RTmean*) proceeded at different rates for the 4 target locations. To answer whether trajectories were systematically grouped, the AIC values of the following 4 models were compared. A 1-term model with a single trajectory representing all target locations ('Combined' model), a 2-term model with separate trajectories for left and right targets ('Left top & bottom/Right top & bottom' model), a 2-term model with separate trajectories for top and bottom targets ('Top left & right/Bottom left & right' model), and a 4-term model with response time trajectories for each of the four target locations ('Separate' model). Results (Table 4.3.1) revealed that the 'Left/Right' model provided the best description of simple reaction time development (AIC*w* = .702). The model with different trajectories for all four target locations ('Separate' model) enjoyed less support than the 'Left/Right' model, but did have some degree of support. The 'Combined' and 'Top/Bottom' models were poor. This means that healthy

development occurred at different rates for targets presented to the left and right of the screen centre.

Table 4.3.1: Healthy controls simple reaction time - AIC condition comparison

RTmean Model	ΔAIC	AIC*w*	Evidence ratio
Left/Right	0	.702	1
Separate	1.9	.386	2.6
Combined	7.1	.020	34.8
Top/Bottom	9.8	.005	134.3

Based on the 'Left/Right' model, the fit of developmental trajectories to linear, quadratic or plateau functions was analysed separately for left and right targets. For both left and right targets, results indicated that plateau functions provided the best description of development (Table 4.3.2). This is because of the downward sloping curves (Figure 4.3.1) that characterise development, where the majority of developmental change occurred during the first few years of development, and little to no development occurred during later years. In addition, the difference in intercept parameters (Table 4.3.2) underlines the necessity for separate developmental trajectories for left and right targets; at the earliest age of measurement response times are slower for right targets (613ms) compared to left targets (566ms). Differences between left and right target response times disappear once reaction times reach their plateau (left = 264ms ; right = 267ms).

Table 4.3.2: Healthy controls simple reaction time - AIC trajectory comparison

Plateau Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Rate Constant	Plateau Term	R^2
Left Targets	21. / <.01	3.1 / .17	0 / .83	566	.02	.264	.62
Right Targets	25.9 / <.01	1.9 / .27	0 / .73	613	.02	.267	.65

Note: Reponses recorded in milliseconds

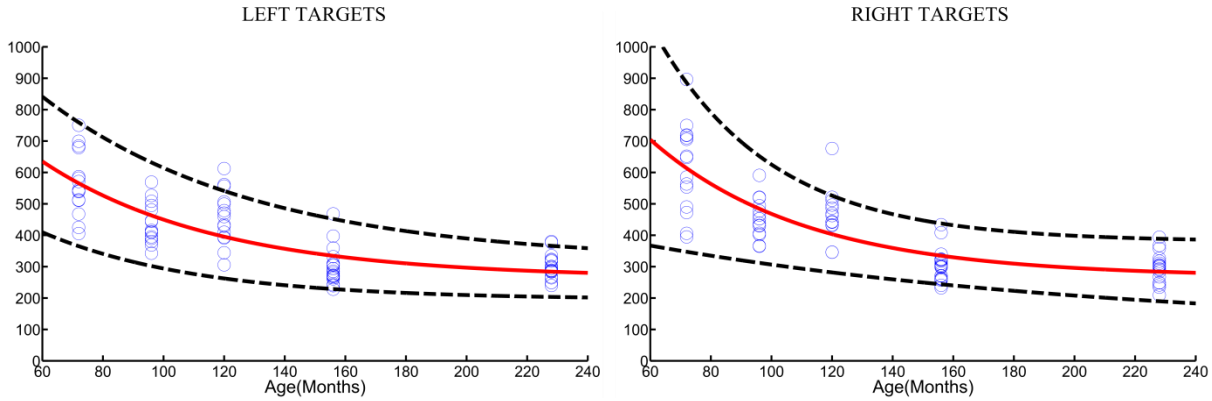


Figure 4.3.1: Healthy controls simple reaction time developmental trajectories. Development of healthy developing controls (blue dots) shown for left and right targets. The developmental trajectories (red solid line) are expressed as plateau functions. 95% CI (dashed black line) are also presented.

Visual Search Task

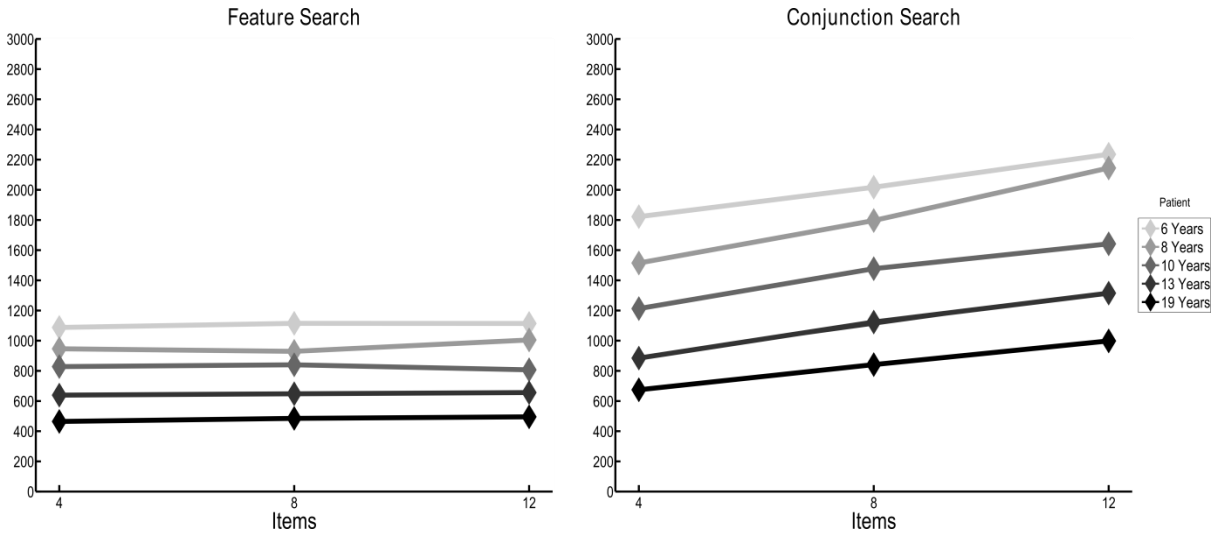


Figure 4.3.2: Healthy controls visual search mean search times. Mean response latencies (ms) of the different age groups for each set size for feature search (left panel) and conjunction search tasks (right panel).

Results for healthy developing controls on the visual search set size conditions are presented in Figure 4.3.2. Older participants demonstrated faster mean visual search times than younger participants in both feature and conjunction search tasks. It is also evident that the response time patterns for feature and conjunction search tasks that are typically observed in healthy individuals are present in the current sample; response time only increases as a function of set size for conjunction search but not feature search. In addition, search efficiency changed relatively little compared to the constant offset between ages. This is shown in the devopmental change which moves the mean search time slopes down without affecting the gradient of slopes. Therefore, developmental differences do not appear to be related to the efficiency of item-by-item processing, but rather to the maturation of processes that are not sensitive to the number of items, such as decision time or response preparation.

To identify whether search efficiency (*VSslope*) developed at different rates on feature and conjunction tasks, an AIC comparison was conducted to test the 3-way interaction between *Task, Setsize* and *Age*. Here, a model which included an 3-way interaction term was

better (AIC*w* = .908) than a null-model (ΔAIC = 4.6 ; AIC*w* = .091). This means that the efficiency of search developed differently on the feature and conjunction search tasks. To answer how search efficiency developed differently on the feature and conjunction search, separate AIC comparisons were conducted for each task examining the 2-way interactions between *Setsize* and *Age*. When compared to null-models, there was minimal evidence of a slope change for feature search (test-model: ΔAIC = 1.9 ; AIC*w* = .28, null-model: ΔAIC = 0 ; AIC*w* = .72) and substantial evidence of slope changes in on conjunction search (test-model: ΔAIC = 0 ; AIC*w* = .95, null-model: ΔAIC = 20 ; AIC*w* = .05). This suggests that the efficiency of search was likely to change with age for conjunction search but not feature search. Finally, an AIC comparison testing the 2-way interaction between *Task* and *Age* was evaluated to determine if the development of mean response time (collapsed across set-size) differed between the 2 tasks. Results revealed an interaction model to be better (AIC*w* = .999) than a null-model (ΔAIC = 116.5 ; AIC*w* < .001). Together these results suggest that changes with age in conjunction search were larger than in feature search for mean search time (*VSmean*) and search efficiency (*VSslope*).

The fit of *VSmean* and *VSslope* developmental trajectories to linear, quadratic or plateau functions was analysed separately for feature and conjunction search tasks (Table 4.3.3).

Table 4.3.3: Healthy controls visual search task - AIC trajectory comparison

Quadratic Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Linear Term	Quadratic Term	R^2
FS – *VSmean*	13.3 / <.01	0 / .57	.5 / .43	1132	-7.424	.021	.79
CS – *VSmean*	16.6 / <.01	0 / .69	1.5 / .31	2074	-15.010	.045	.77

Linear Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates		Fit Summary
	Linear	Quadratic	Plateau	Intercept	Slope	R^2
FS – *VSslope*	0 / .63	1.1 / .38	-	3	-.007	< .01
CS – *VSslope*	0 / .67	1.4 / .33	-	64	-.142	< .01

Notes: FS: Feature Search, CS: Conjunction Search, reponses recorded in milliseconds

For *VSmean*, the relative likelihood that development was characterised by either a quadratic or plateau function was nearly equivalent (ΔAIC < 2) on both feature and conjunction search. *VSmean* linear functions produced very poor fits. The quadratic functions explained a large proportion of variance (FS (R^2) = .786 ; CS (R^2) = .766), therefore, overall feature and conjunction search time offered a sensitive measure of developmental change. The model parameters of the two *VSmean* quadratic functions (Table 4.3.3) capture the differences in development between feature and conjunction search. *VSmean* at the earliest age of measurement (intercept) was much higher for conjunction search (2074ms) than feature search (1132ms). In addition, the rate of development (linear term) was greater for conjunction search (-15ms each month) in comparison to feature search (-7ms each month). Finally, the dominance of nonlinear functions can be further explained by the downward sloping curve that characterises the developmental change of *VSmean* (Figure 4.3.3**,** top

panels). For both trajectories the majority of developmental change occurred during the early years, while developmental change at later years was minimal.

For *VSslope*, the relative likelihood of linear and quadratic functions was almost equivalent ($\Delta AIC < 2$) for feature and conjunction search. Model parameters of the linear functions capture the developmental differences in visual search proficiency between feature and conjunction search tasks. First, at the youngest age of measurement (intercept term) participants required more time for each addition search item for conjunction search (64ms per item) than feature search (3ms per items). Second, the rate of search efficiency development (slope term) was greater for the conjunction search (-.142ms each month) than feature search tasks (-.007ms each month). Finally, Figure 4.3.3 (bottom panels) shows that search proficiency improved marginally with age for conjunction search and was static for feature search. In addition, feature and conjunction search efficiency is much more variable at younger ages than at older ages.

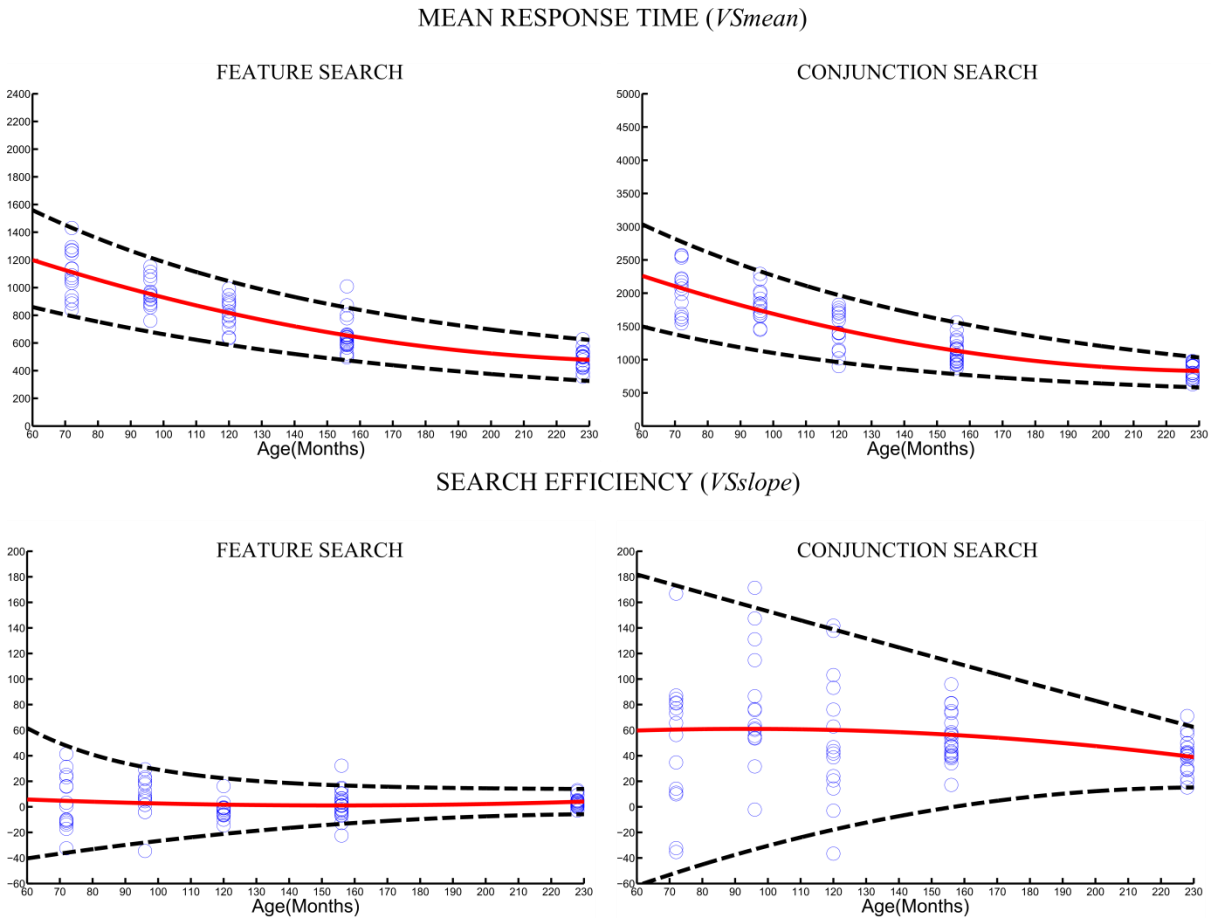


Figure 4.3.3: Healthy controls visual search developmental trajectoies. Mean reaction time (*VSmean*) and search efficiency (*VSslope*) of healthy developing controls (blue dots) during the visual search task for feature and conjunction search conditions. Based on the Developmental trajectories for controls (red solid line) are expressed as quadratic and linear functions for *VSmean* and *VSslope* respectively. 95% CI (dotted black line) are also presented.

4.4 Language

Participants:

Control data for the language tasks was collected from a sample of 104 children, teenagers and young adults (age range: 72 – 228 months). Data was collected from primary schools, secondary schools and undergraduate psychology students. Prior to testing, informed consent was taken from undergraduate students or from parents of children who took part from primary or secondary school.

Production and Comprehension

Verbal production and comprehension performance were measured through the Boston-Naming Task (*BNT*) and British Picture Vocabulary Scale (*BPVS*). The AIC comparison of linear, quadratic and plateau function fits to the *BNT* and *BPVS* developmental data revealed that quadratic functions offered the best description of development (Table 4.4.1).

Table 4.4.1: Healthy controls verbal production and comprehension - AIC trajectory comparison

Quadratic Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Linear Term	Quadratic Term	R^2
BNT	4.6 / .05	0 / .51	0.4 / .43	384	-2.447	.005	.83
BPVS	0.6 / .28	0 / .38	0.1 / .34	573	-6.074	.002	.84

For *BNT* performance, the relative likelihood of a quadratic and plateau was nearly equivalent (ΔAIC < 2), suggesting that developmental change was nonlinear. Figure 4.4.1 shows that the majority of developmental change occurred during earlier years (6 – 10 years). In contrast,

the relative likelihood between the 3 functions was minimal for *BPVS* development (ΔAIC < 1). However, based on an inspection of raw scores (Figure 4.4.1) a quadratic model was deemed as the most appropriate fit. This is because improvements in verbal comprehension are unlikely to increase linearly past the age of 19 years. Finally, changes in age explained a large proportion on the performance variance observed in *BNT* (R^2 = .834) and *BPVS* (R^2 = .839) suggesting these tasks are sensitive to developmental effects.

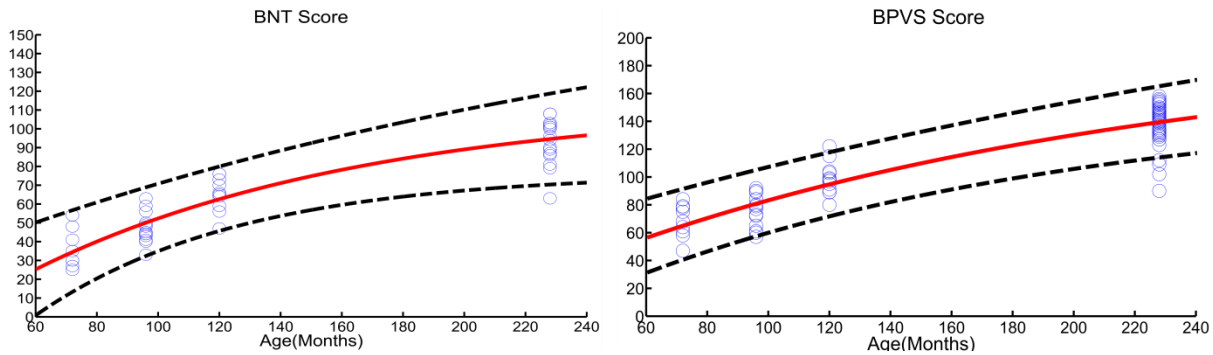


Figure 4.4.1: Healthy controls verbal production and comprehension developmental trajectories. *BNT* and *BPVS* performance of healthy developing controls (blue dots). Developmental trajectory for controls is expressed as a non-linear plateau function (red solid line). 95% CI (dotted black line) are also presented.

Non-word Learning Task

The non-word naming task examined the total number of non-words (max 30) participants are able to verbally produce (*NonProd*) and comprehend (*NonComp*) during a sequence of 6 learning iterations. The mean performance of the different age groups across these learning iterations is displayed in Figure 4.4.2.

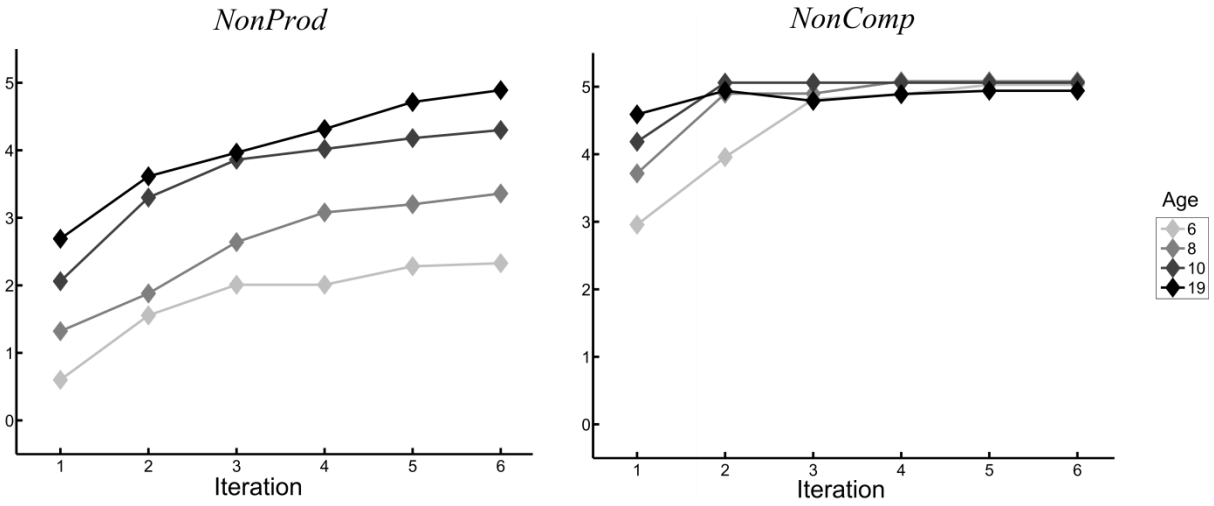


Figure 4.4.2: Healthy controls mean non-word production and comprehension scores. Mean number of monsters named and identified for production (left) and comprehension (right) respectively by healthy controls. The learning phase is represented by the initial 6 iterations.

Differences between the age groups for the production and comprehension of non-words appeared evident. Specifically, during the first iteration of the learning phase, older participants are able to produce / comprehend more non-words. In terms of the rate of learning across the learning iterations (iteration 1 – 6), it is unclear whether the age groups exhibited differences for non-word production and comprehension. For the developmental trajectory comparisons, linear, quadratic and plateau functions were fitted to *NonProd* and *NonComp* measures separately. The comparison of AIC values for the linear, quadratic, and plateau functions (Table 4.4.2) revealed that development was best defined by plateau functions for both *NonProd* (AIC*w* = 0.428) and *NonComp* (AIC*w* = 0.565), but the relative

likelihood that development was described by a quadratic function was essentially equivalent (ΔAIC < 1) to the likelihood of a plateau function on both measures. Linear functions provided fits that were substantially less likely than the nonlinear functions (ΔAIC > 2). Changes in age explain a relatively large proportion of variance observed in both production (R^2 = .503) and comprehension (R^2 = .378). Model parameters of the two plateau models highlight differences in development between *NonProd* and *NonComp*. At the youngest age of measurement (intercept term) comprehension (26 monsters) was better than the production (12.5 monsters). Similarly, comprehension (29 monsters) was better than production (26 monsters) at the peak of development (plateau term).

Table 4.4.2: Healthy controls non-word learning - AIC trajectory comparisons

Plateau Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Rate Constant	Plateau	
NonProd	2.1 / .15	0.1 / .42	0 / .43	12.558	.035	25.951	.50
NonComp	13.8 / <.01	0.5 / .44	0 / .56	26.064	.048	29.064	.38

The upward sloping developmental curves presented in Figure 4.4.3 further explain the preference of nonlinear functions. The majority of development occurred rapidly during younger ages and plateaued after the age of 10 years. This effect was more prominent for *NonProd* than *NonComp*. However this is likely to be due to ceiling effects present in the latter measure.

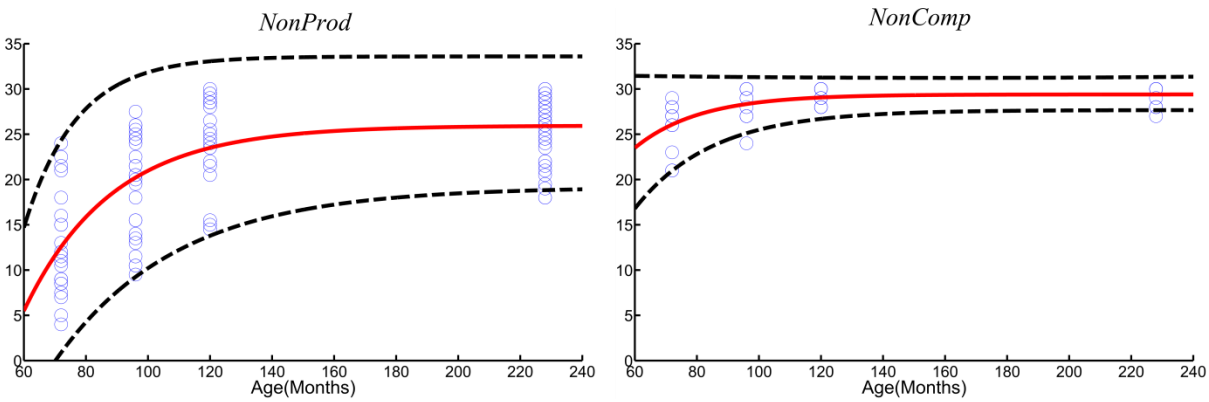


Figure 4.4.3: Healthy controls non-word developmental trajectories. Developmental trajectories for the sum of monsters named (production; left panel) and recognised (comprehension; right panel) during the learning phase. Both trajectories were best defined by a plateau model. 95% CI (dotted black line) are also presented.

4.5 OculoMotor

Participants:

Control data for the oculomotor tasks was collected from a sample of 265 children, teenagers and young adults (age range: 72 – 228 months). Data was collected from primary schools, secondary schools and undergraduate psychology students. Prior to testing, informed consent was taken from undergraduate students or from parents of children who took part from primary or secondary school.

Fixation Task

The healthy development of fixation duration (*FixDwell*) and intrusive saccade frequency (*FixSacc*) was examined based on fixations to 4 horizontal and vertical targets. For fixation duration (*FixDwell*), an AIC comparison was conducted to test the 2-way interaction between *TargetLocation* and *Age*. Here a model which included an interaction term (ΔAIC = 0; AIC*w* = .99) was better than a model that did not (ΔAIC = 46; AIC*w* <.01). This means the rate which sustained fixation duration developed was different for the four target locations. To answer whether trajectories were systematically grouped the AIC of the

following 5 models were compared: a 4-term model with a separate trajectory for each of the four target locations (‘Separate’ model), and four 2-term models where development only differed for a single target location (‘Left’,’Right’,’Top’,’Bottom’ models). Results (Table 4.5.1) revealed that the ‘Separate’ and ‘Top’ model provided essentially equivalent descriptions of sustained fixation development (AIC*w* = .50). The relative likelihood of the remaining models was poor. This means that healthy development occurs at a different rate for top targets in comparison to targets presented in the other three locations

Table 4.5.1: Healthy controls fixation duration - AIC condition comparisons

Model	ΔAIC	AIC*w*	Evidence ratio
Separate	0	.50	1
Top	.1	.50	1
Bottom	20	<.01	>1000
Left	28	<.01	>1000
Right	31	<.01	>1000

Based on the ‘Top’ model, the fit of the developmental trajectories to linear, quadratic or plateau functions was analysed separately for the top target location; the development of left, right, and bottom targets were combined (‘L / R / B’ development). Results indicated that plateau functions clearly offered the best description of development for both the top target and the remaining targets (Table 4.5.2). This is because of the upward sloping curves (Figure 4.5.1) that characterise development, where the majority of developmental change occurred during the early years of development, and little to no development occurred during later years. In addition, the difference in intercept parameters underlines the necessity for development to be defined separately for top targets; at the earliest age of measurement fixation duration are higher for top targets (4319ms) compared to the other targets (4001ms).

Differences between target locations disappear once fixation durations reach their plateau (top= 4891ms ; L / R / B = 4923ms).

Table 4.5.2: Healthy controls fixation duration - AIC trajectory comparisons

Plateau Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Rate Constant	Plateau	R^2
Top	23.6 / <.01	8.3 / .01	0 / .98	4319	.08	4891	.153
L / R / B	53.49 / <.01	10.1 / <.01	0 / .99	4001	.05	4923	.382

Note: Durations recorded in milliseconds

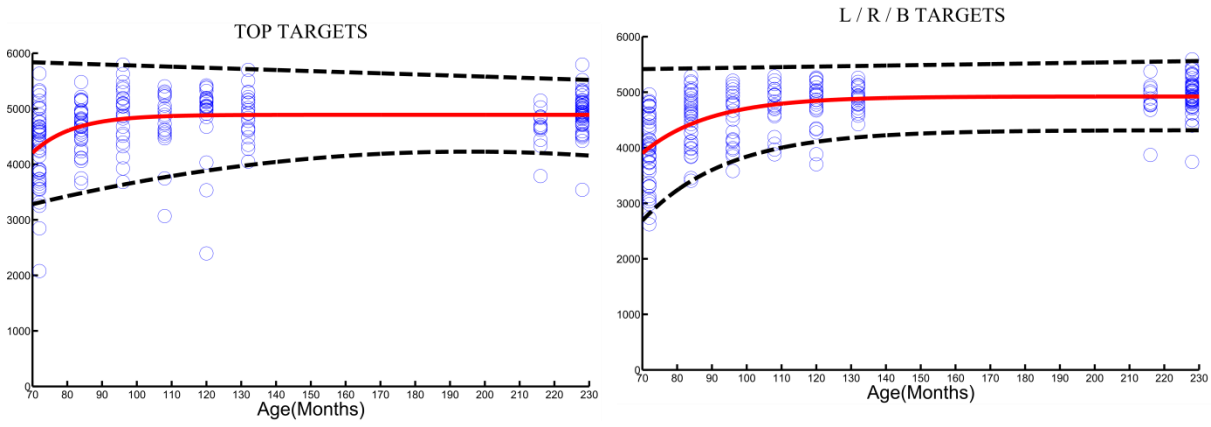


Figure 4.5.1: Healthy Controls fixation duration developmental trajectories. Mean fixation duration time (*FixDwell*) of healthy developing controls (blue dots). Development is best expressed by a plateau function (red line). Developmental trajectories were defined for top target and the remaining target ('L / R / B' target) separately. 95% CI (dotted black line) are also presented.

For the frequency of intrusive saccades during fixation (*FixSacc*), an AIC comparison was conducted to test the 2-way interaction between *TargetLocation* and *Age*. Here a model which included an interaction term (ΔAIC / AIC*w* = 0 / .98) was clearly better than a model that did not (ΔAIC / AIC*w* = 8 / .02). Therefore, the rate that intrusive saccade suppression

develops differed between the four target locations. To answer whether trajectories were systematically grouped, the same 5 models from the *FixDwell* analysis were compared. Again, results (Table 4.5.3) revealed that the 'Top' (ΔAIC / AIC*w* = 0 / .58) and 'Separate' (ΔAIC / AIC*w* = .7 / .41) models offered the essentially equivalent descriptions of development. The remaining models were poor in comparison. This suggests that healthy development occurs at a different rate for top targets in comparison to targets presented in the other three locations.

Table 4.5.3: Healthy controls intrusive saccades – AIC condition comparisons

Fix*Dwell* Model	ΔAIC	AIC*w*	Evidence ratio
Top	0	.58	1
Separate	.7	.41	1.4
Left	11	<.01	257
Right	26	<.01	>1000
Bottom	29	<.01	>1000

Based on the 'Top' model, the fit of the developmental trajectories to linear, quadratic or plateau functions was analysed separately for the top target location; left, right, and bottom targets were combined ('L / R / B' development). Similar to *FixDwell*, results indicated that plateau functions clearly offered the best description of development for both the top target and the remaining targets (Table 4.5.4). This is because of the downward sloping curves (Figure 4.5.2) that characterise development, where the majority of developmental change occurred during the first few years of development, and little to no development occurred during later years. In addition, the difference in intercept parameters underlines the necessity for development to be defined separately for top targets; at the earliest age of measurement intrusive saccades are less frequent for top targets (1.73) compared to the other targets (2.03).

Differences between target locations disappeared once the frequency of saccades reached the plateau of development (top= 1.06 ; L / R / B = 1.05).

Table 4.5.4: Healthy controls intrusive saccades – AIC trajectory comparisons

Plateau Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Rate Constant	Plateau	R^2
Top	14.1 / <.01	1.2 / .35	0 / .65	1.73	.03	1.06	.242
L / R / B	53.49 / <.01	10.1 / <.01	0 / .99	2.03	.03	1.05	.417

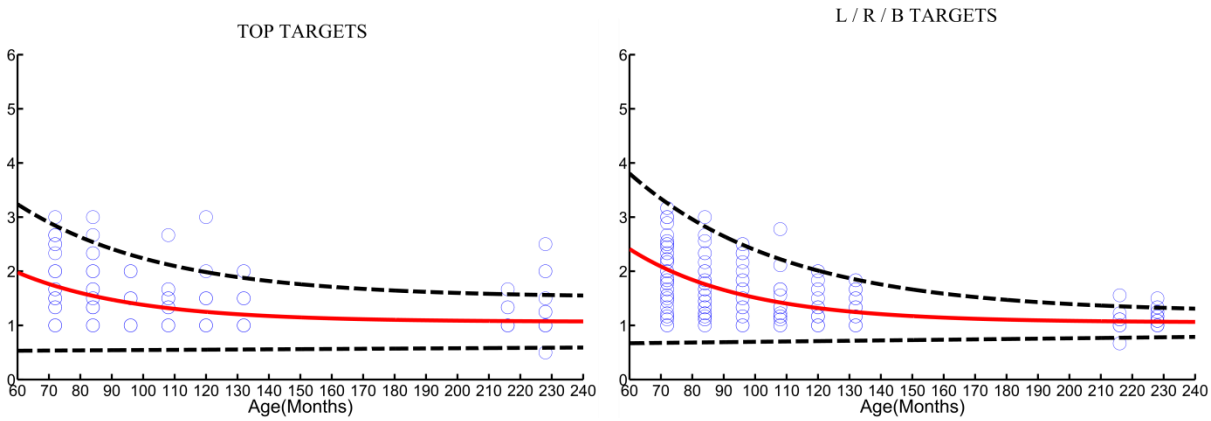


Figure 4.5.2: Healthy controls intrusive saccade developmental trajectories. Mean frequency of intrusive saccades (*FixSacc*) of healthy developing controls (blue dots). Development is best expressed by plateau functions (red line). Developmental trajectories were defined for top target and the remaining target ('L / R / B' target) separately. 95% CI (dotted black line) are also presented.

Prosaccade Task

The development of 2 saccade parameters was examined for the pro-saccade task: latency of saccade initiation (*SaccOnset*) and saccade velocity (*SaccVelo*). AIC comparisons of the 2-way iterations between *Targetlocation* and *Age* for *SaccOnset* (test-model (ΔAIC / AIC*w*) = 0 / .99 ; null-model (ΔAIC / AIC*w*) = 46 / <.01) and *SaccOnset* (test-model (ΔAIC / AIC*w*) = 0 / .92 ; null-model (ΔAIC / AIC*w*) = 5 / .08) revealed that development did not occur uniformly across the 8 target locations on either task. In order to answer how development differed between target locations, the 5 following models were compared: A 1-term model with a single trajectory representing performance collapsed across target locations ('Combined' model), a 2-term model with separate trajectories for inner and outer target amplitudes ('Amplitude' model), a 2-term model with separate trajectories for vertical and horizontal target locations ('Hori / Vert' model), a 4-term model with a separate trajectory for each four target directions (left, right, up, down; 'Direction' model), and a 8-term model with a trajectory for each of the eight target locations ("Separate" model). AIC comparisons of the two pro-saccade measures are presented in Table 4.5.5. AIC comparison of the Sacc*Onset* and Sacc*Velo* model sets revealed that the best description of development across target location was offered by the "Separate" model (Sacc*Onset*: AIC*w* = .999; Sacc*Velo*: AIC*w* = .999). For both measures, the evidence ratios demonstrated the 'Separate' model to be over 1000 times more likely than the 4 remaining models.

Table 4.5.5: Healthy controls pro-saccade task – AIC condition comparisons

Sacc*Onset* Model	ΔAIC	AIC*w*	Evidence ratio
Separate	0	.999	1
Directions	155	<.001	> 1000
Hori / Vert	200	<.001	> 1000
Amplitude	259	<.001	> 1000
Combined	400	<.001	> 1000
Sacc*Velo* Model	ΔAIC	AIC*w*	Evidence ratio
Separate	0	.999	1
Amplitude	109	<.001	> 1000
Directions	1161	<.001	> 1000
Hori / Vert	1191	<.001	> 1000
Combined	1222	<.001	> 1000

To find the best developmental trajectories of saccade initiation latency (*SaccOnset*), the fit of linear, quadratic and plateau models were compared based on the 'Separate' model (separate trajectories for each target). Results (Table 4.5.6) found that plateau functions were best (ΔAIC = 0) for 7 of the 8 target locations, while a linear function was best for a single target location (inner right). The likelihood that development followed a nonlinear trajectory for the 7 target locations is further explained by the downward sloping curves characterised Sacc*Onset* development (Figure 4.5.3). The rate of development decreased as a function of age, whereby little or no differences were observed between the performance of the older participants (age 18 – 19 years). In addition, the model parameter estimates shown in Table 4.5.4 highlight the necessity of target-specific developmental trajectories. Notably, a pattern between model intercepts emerged based on target amplitude and direction; The latency of saccade onsets were always shorter for inner versus outer targets, and latency increased for direction based on the following order: right, left, top, bottom. A similar pattern was evident

for the plateaus, whereby latencies were shorter for inner versus outer target amplitudes. The effects of target direction was less clear, but saccade latencies for bottom targets were greater than targets presented at other locations with the same amplitude. Rates in development (as expressed by rate constants) did not appear to differ systematically between target locations. Together these trends suggest that the speed in which children and adults program and execute saccades can be influenced by target direction and amplitude.

Table 4.5.6: Healthy controls pro-saccade onset – AIC condition comparisons

Linear Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Slope		R^2
Inner Right	0 / .57	2 / .21	2 / .21	195	-.311	-	.27

Plateau Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Rate Constant	Plateau	R^2
Inner Left	8.5 / < .01	0.8 / .39	0 / .60	217	.021	149	.22
Inner Top	.88 / .24	0.1 / .37	0 / .38	223	.010	142	.22
Inner Bottom	1.81 / .18	0.3 / .36	0 / .46	255	.012	163	.23
Outer Right	6.6 / .03	1.4 / .31	0 / .66	236	.013	152	.34
Outer Left	15.31 / < .01	3.7 / .14	0 / .86	247	.022	162	.33
Outer Top	3.9 / .07	.46 / .41	0 / .52	268	.015	177	.23
Outer Bottom	13.9 / < .01	.92 / .38	0 / .61	299	.016	176	.41

Note: Saccade onets recorded in milliseconds

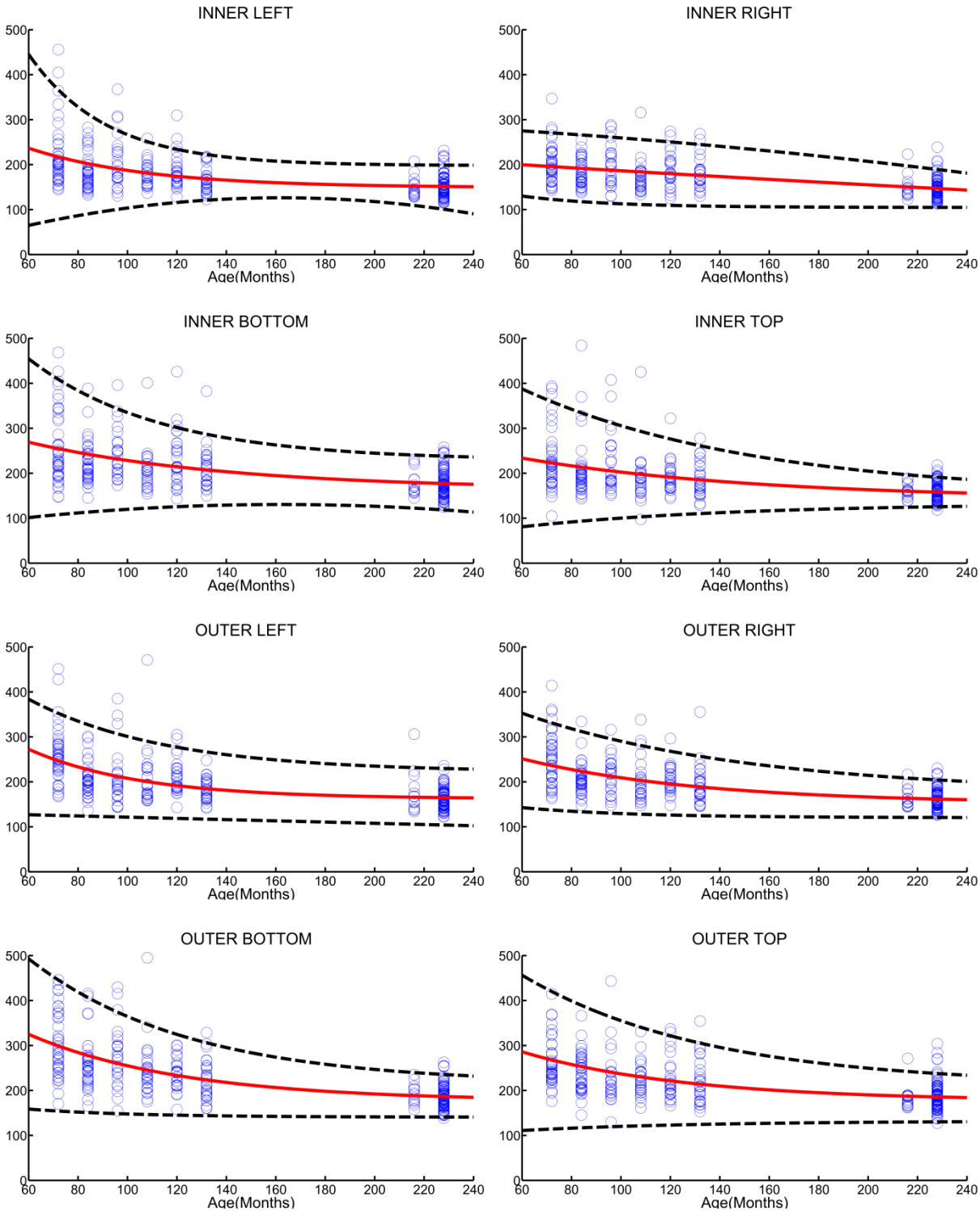


Figure 4.5.3: Healthy controls saccadic onset development trajectories. Mean saccadic onset time of healthy developing controls (blue dots) during the pro-saccade task. Onset time is presented for each of the 8 target locations. 95% CI (dotted black line) are also presented.

The comparison of saccade velocity (*SaccVelo*) developmental trajectories to linear, quadratic and plateau functions was based on the 'Separate' model. Therefore, separate trajectories were defined for each target location. Results (Table 4.5.7) revealed that saccade velocity development was best defined (ΔAIC = 0) by quadratic functions for 7 of the 8 target locations, while a single target location (outer right) was best defined by a linear function. The relative likelihood of a quadratic function for 6 target locations (inner left, inner right, inner top, inner bottom, outer left, outer top) was considerable (AIC*w* range = .804 – .999). In addition, for 2 target locations (outer right, outer bottom) the relative likelihood between a quadratic and linear trajectory was equivalent (ΔAIC < 2). Plateau functions could not be fitted to 4 target locations (inner bottom, outer right, outer top and outer bottom) due to the inability to obtain accurate intercept and plateau parameter estimates. However the effects of age on Sacc*Velo* were unclear. The proportion of variance in Sacc*Velo* that was explained by age was less than 10% for all target locations. In addition the examination of the linear slope terms for linear and quadratic functions revealed that the 95% confidence limits crossed 0. Therefore, it is unclear whether age-related changes for saccade velocity occured within the age range (6 – 19 years) of the current sample. The saccade velocity developmental slopes of the 8 target locations (Figure 4.5.4) further demonstrate the minimal change in performance as a function of age.

Table 4.5.7: Healthy controls pro-saccade velocity – AIC trajectory comparisons

Linear Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Slope		R^2
Outer Right	0 / .54	0.8 / .37	3.5 / .10	386	-.065	-	< .01

Quadratic Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Linear Term	Quadratic Term	R^2
Inner Left	5.5 / .06	0 / .94	-	252	-.534	.004	.05
Inner Right	4.4 / .10	0 / .90	-	274	-.578	.004	.03
Inner Top	16.3 / < .01	0 / .99	-	296	-1.349	.008	.06
Inner Bottom	10.5 / < .01	0 / .974	7.7 / .02	306	-1.138	.006	.04
Outer Left	2.8 / .20	0 / .80	-	350	-.545	.003	.02
Outer Top	7.5 / .02	0 / .88	4.4 / .10	422	-1.507	.008	.05
Outer Bottom	0.6 / .30	0 / .42	0.7 / .28	423	-.919	.004	.05

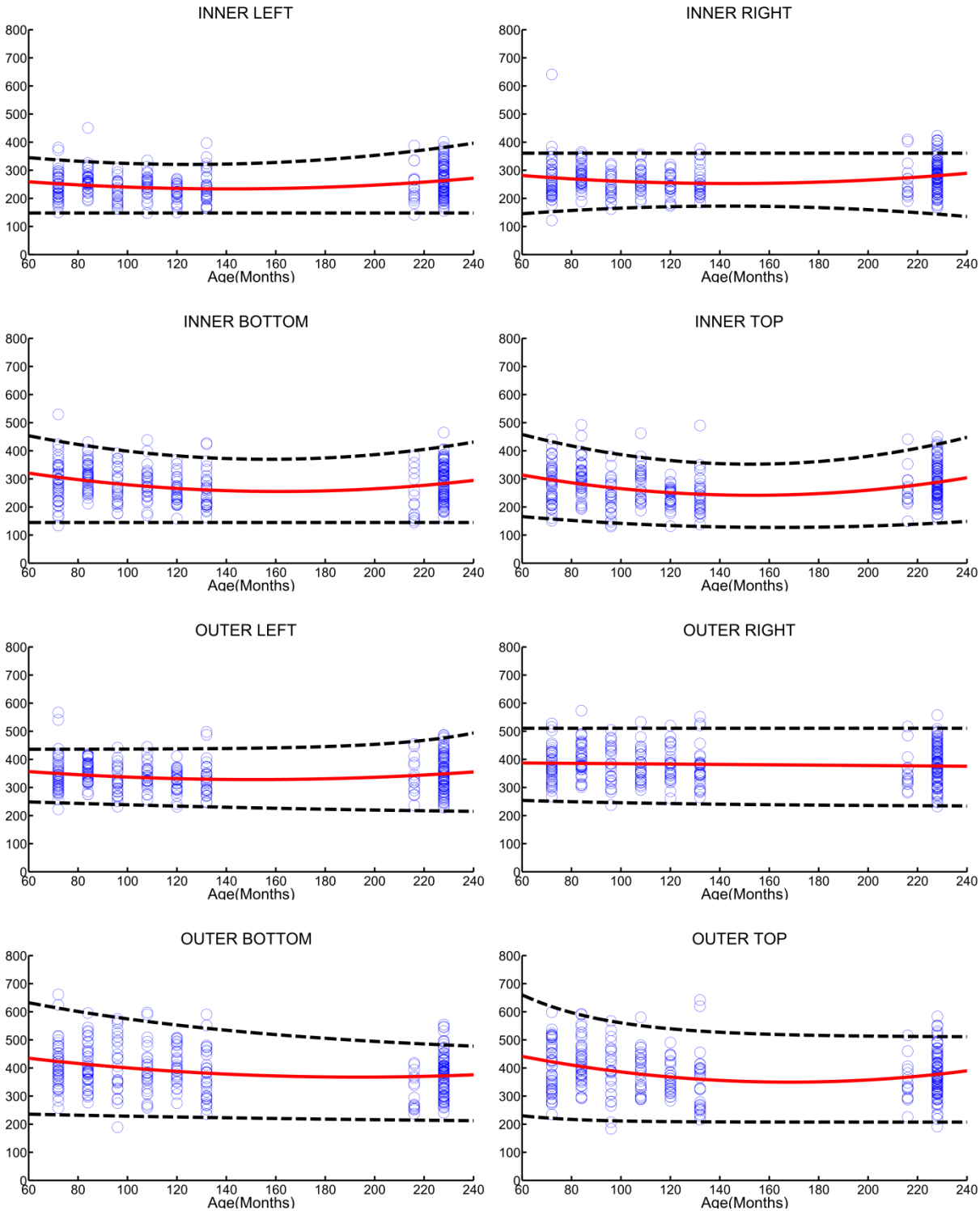


Figure 4.5.4: Healthy controls saccade velocity developmental trajectories. Mean saccade velocity (*SaccVelo*) of healthy developing controls (blue dots) during the pro-saccade task. Saccade velocity is presented for each of the 8 target locations. 95% CI (dotted black line) are also presented.

Anti-saccade Task

The development of 3 measures was examined during the anti-saccade task: The time taken for the participant's gaze to reach the anti-saccade location (*AntiOffset*), the proportion of pro-saccade errors (*AntiErr*), and the proportion of corrected errors (*AntiCorr*). AIC comparisons of the 2-way iteration between *Targetlocation* and *Age* revealed that development was not uniform across target locations for *AntiOffset* (test-model (ΔAIC / AIC*w*) = 0 / .99 ; null-model (ΔAIC / AIC*w*) = 46 / <.01), *AntiErr* (test-model (ΔAIC / AIC*w*) = 0 / .82 ; null-model (ΔAIC / AIC*w*) = 3 / .18) and *AntiCorr* (test-model (ΔAIC / AIC*w*) = 0 / .92 ; null-model (ΔAIC / AIC*w*) = 14 / .08). As with the pro-saccade task, five models were set up and compared to determine the best model describing the developmental trajectories of these measures. AIC comparisons are presented in Table 4.5.8.

Table 4.5.8: Healthy controls anti-saccade task – AIC condition comparisons

Anti*Offset* Model	ΔAIC	AIC*w*	Evidence ratio
Separate	0	.999	1
Amplitude	34	<.001	> 1000
Hori / Vert	107	<.001	> 1000
Directions	110	<.001	> 1000
Combined	136	<.001	> 1000
Anti*Err* Model	**ΔAIC**	**AIC*w***	**Evidence ratio**
Separate	0	.999	1
Amplitude	26	<.001	> 1000
Directions	66	<.001	> 1000
Combined	85	<.001	> 1000
Hori / Vert	92	<.001	> 1000
Anti*Corr* Model	**ΔAIC**	**AIC*w***	**Evidence ratio**
Directions	0	.556	1
Seperate	.976	.341	1.629
Hori / Vert	3.748	.085	6.513
Combined	6.962	.017	32.493
Amplitude	14.373	<.001	1324

Based on the ‘Separate’ model, the fit of *AntiOffset* developmental trajectories to linear, quadratic or plateau functions was analysed separately for the 8 target location. Results (Table 4.5.9) found that quadratic functions offered the best description of development for the 7 of the 8 target locations, while for the outer left target development was best described by a plateau function. For all target locations the relative likelihood between quadratic or plateau functions was minimal (AIC < 2), with both functions providing accurate descriptions of development. Changes in age explained a large proportion of Anti*Offset* variance (R^2 range = .477 - .622) across target locations. The dominance of nonlinear models is further explained by the downward sloping curves that characterise Anti*Offset* development (Figure 4.5.5).

Table 4.5.9: Healthy controls anti-saccade offset – AIC trajectory comparisons

Quadratic Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Linear Term	Quadratic Term	R^2
Inner Left	12.5 / <.01	0 / .59	0.7 / .41	819	-4.729	.014	.62
Inner Right	20.9 / <.01	0 / .52	0.2 / .48	842	-5.592	.019	.62
Inner Bottom	8.2 / .01	0 / .63	1.1 / .37	852	-4.839	.015	.48
Inner Top	11.2 / <.01	0 / .67	1.4 / .33	875	-4.855	.016	.52
Inner Bottom	8.2 / .01	0 / .63	1.1 / .37	852	-4.839	.015	.48
Outer Right	12.2 / <.01	0 / .61	0.9 / .39	881	-4.448	.013	.62
Outer Bottom	8.37 / <.01	0 / .56	0.5 / .43	901	-4.322	.014	.48
Outer Top	8.1 / <.01	0 / .55	0.4 / .44	922	-4.886	.015	.49

Plateau Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Rate Constant	Plateau	R^2
Outer Left	11.7 / <.01	0.1 / .49	0 / .51	882	.012	435	.58

Note: Anti-saccade offsets recorded in milliseconds

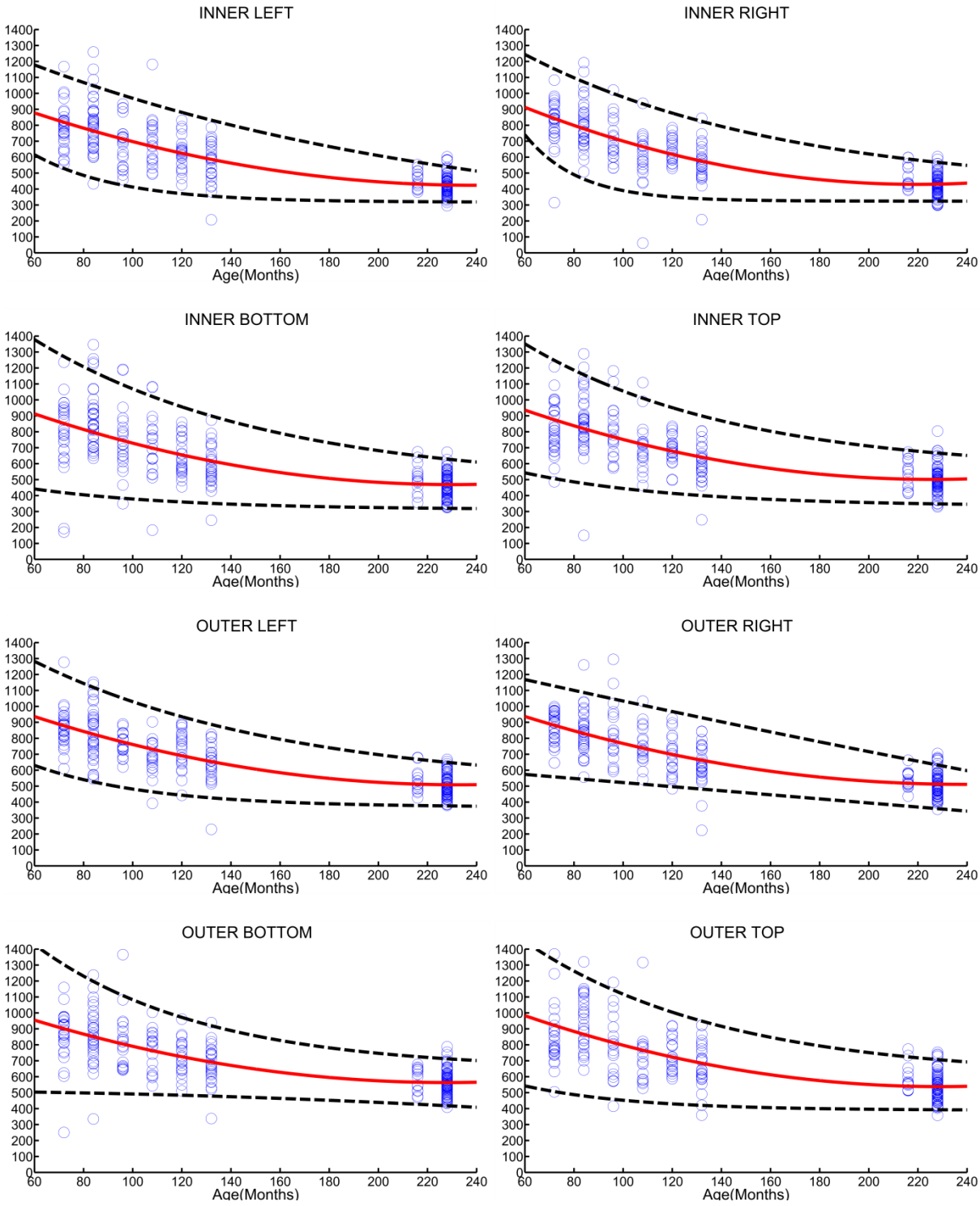


Figure 4.5.5: Healthy controls anti-saccade offset developmental trajectories. Mean target offset time (Anti*Offset*) of healthy developing controls (blue dots) during the anti-saccade task. Offset time is presented for each of the 8 target locations. 95% CI (dotted black line) are also presented.

The rate of Anti*Offset* development decreased as a function of age, whereby developmental change occurred among the younger participants (age 6 – 11 years) and little to no differences were observed between the performance of the older participants (age 18 – 19 years). In addition, the rates of development appeared to be more prominent for Anti*Sacc* than the developmental rates reported for *SaccOnset*, where curves were very shallow. This suggests that Anti*Sacc* developments reflect improvements in the top-down attentional processes involved in response inhibition and the execution of endogenously guided saccades. Finally, differences between the model parameters (Table 4.5.9) of the different trajectories highlight the need for target-specific developmental trajectories. Similar to Sacc*Onset*, there was a trend for the intercepts of Anti*Sacc* to have latencies that were shorter for inner vs. outer and horizontal vs. vertical targets.

AIC comparison of developmental trajectories (linear, quadratic, or plateau) for the proportion of anti-saccade errors (*AntiErr*) is presented in Table 4.5.10. The analysis is based on the 'Separate' model (Table 4.5.6) therefore developmental trajectories were created for each of the 8 target locations.

Table 4.5.10: Healthy controls anti-saccade error production – AIC trajectory comparisons

Linear Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates		Fit Summary
	Linear	Quadratic	Plateau	Intercept	Slope	R^2
Inner Bottom	0 / .51	0.1 / .49	-	.892	-.036	.36
Outer Left	0 / .68	1.5 / .32	-	.921	-.045	.49
Outer Bottom	0 / .66	1.3 / .34	-	.912	-.043	.50

Quadratic Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Linear Term	Quadratic Term	R^2
Inner Left	3.4 / .16	0 / .84	-	.876	.002	-.003	.36
Inner Right	8.1 / .02	0 / .98	-	.914	.013	-.003	.38
Inner Top	4.6 / .09	0 / .91	-	.888	.008	-.003	.31
Outer Right	1.4 / .33	0 / .67	-	.892	-.015	-.002	.48
Outer Top	6.2 / .04	0 / .96	-	.883	.002	-.003	.46

Three target locations (inner bottom, outer left and outer bottom) were best defined by a linear function and five target locations (inner left, inner right, inner top, outer right and outer top) were best defined by a quadratic function. A quadratic function always provides a pretty good fit, but a linear function does not. The fitting of plateau functions failed for all target locations since obtaining accurate model parameters (constant rate and plateau) was not

possible. All developmental trajectories revealed that changes in age explained a relatively large proportion of variance in Anti*Err* ($R^2 > .30$). For 4 target locations (inner left, inner right, inner top and outer top) the relative likelihood of a quadratic developmental function (compared to linear functions) was substantial (ΔAIC > 3). While the relative likelihood of linear and quadratic functions for the remaining 4 target locations were essentially equivalent (ΔAIC < 2). The developmental curves presented in Figure 4.5.6 further explain the differences in model likelihood. For the target locations where a quadratic developmental trajectory was more likely, little change in performance occurred during the early years of development (6 – 9 years). For the target locations where linear and quadratic developmental trajectories were equivalent, changes in performance occurred earlier on in development.

An important observation for *AntiErr* development was the high proportion of errors that the younger children produced. Model intercepts indicated that at the youngest age children produced at least 87% anti-saccade errors (close to ceiling). In addition, Figure 4.5.6 shows that developmental change does not occur until approximately 10 years of age for many target locations. Furthermore Figure 4.5.6 shows an increase in between-participant variance (as expressed by the widening confidence limits) as a function of age. Here between-participant variance is considerable for the eldest year groups (18 – 19 years). Together, these observations indicated that the difficulty of the task was too high. Young healthy controls were too close to ceiling and the variance in older healthy controls was too large. This means mild impairments of saccade inhibition that could be expressed by patients would likely be masked. Therefore Anti*Err* was not used in the subsequent analysis of patient data in later chapters.

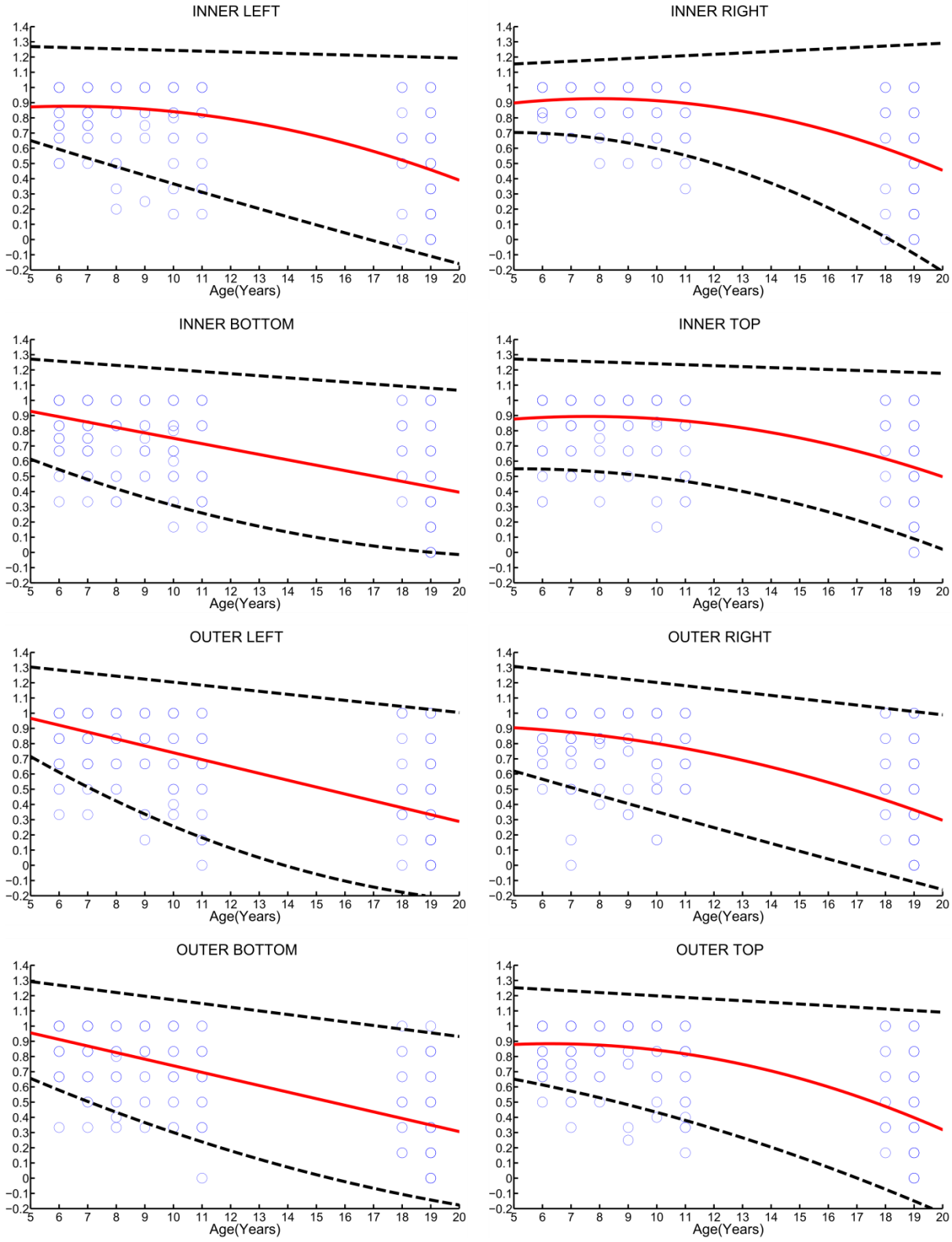


Figure 4.5.6: Healthy controls anti-saccade inhibition developmental trajectories. Proportion of anti-saccade errors (Anti*Err*) of healthy developing controls (blue dots) during the anti-saccade task. Corrected errors are presented for each of the 8 target locations. 95% CI (dotted black line) are also presented.

AIC comparison of developmental trajectories (linear, quadratic, or plateau) for the proportion of corrected errors (Anti*Corr*) is presented in Table 4.5.11. The analysis is based on the 'Direction' model (Table 4.5.6) therefore 4 developmental trajectories were created based on average Anti*Corr* performance across target directions (left, right, top and bottom).

Table 4.5.11: Healthy controls anti-saccade error correction– AIC trajectory comparisons

Plateau Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Rate Constant	Plateau	R^2
Left	4.9 / .06	1.8 / .27	0 / .68	.783	.341	.963	.15
Right	81.1 / <.01	17.5 / <.01	0 / .99	.697	.515	.957	.27
Top	26.6 / <.01	6.2 / .04	0 / .96	.733	.555	.967	.27
Bottom	5.8 / .03	.95 / .37	0 / .60	.687	.233	.961	.23

Developmental trajectories of all target directions were best described a plateau model (ΔAIC = 0) with age explaining at least 15% of variance in Anti*Corr* for the 4 trajectories. The relative likelihood of a plateau model was substantial for the right (AIC*w* = .999) and top (AIC*w* = .957) target directions. Quadratic model was offered reasonable good fits to targets positioned in the left (AIC*w* = .267) and bottom directions (AIC*w* = .370). Linear models produced poor fits for all 4 target directions. The preference of nonlinear models is further clarified by the upward sloping curves presented in Figure 4.5.7. The rate of development is substantial during early years (6 – 8 years) and eventually lessens to a halt at approximately 11 years of age. This is due to the majority of older participants obtaining ceiling scores (100% of errors corrected) and explains why development is described accurately by plateau models. Interestingly, the spread of variance between participants (expressed by the

confidence intervals) indicates that performance is highly variable (between 0 – 100%) for the youngest children and narrows as age increases.

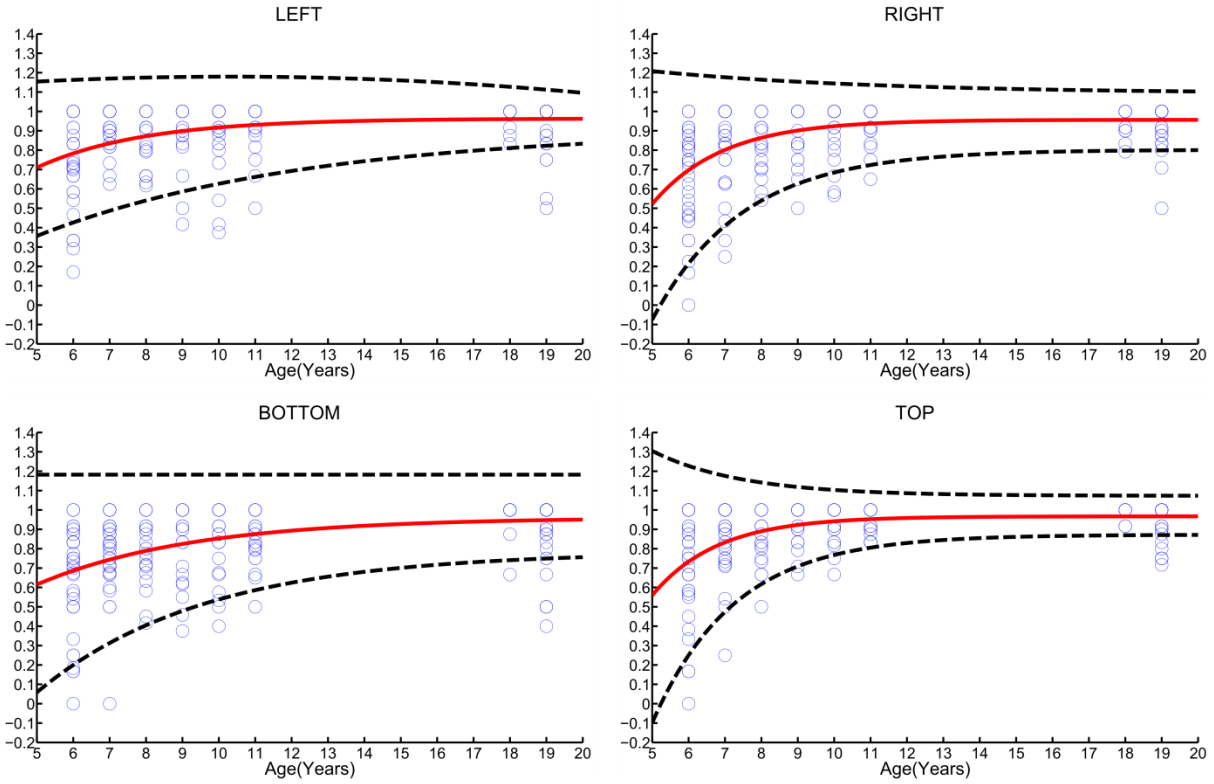


Figure 4.5.7: Healthy controls anti-saccade error correction developmental trajectories. Proportion of corrected errors (*AntiCorr*) of healthy developing controls (blue dots) during the anti-saccade task. Most likely (ΔAIC = 0) developmental trajectories are shown as red lines. Corrected errors are presented the performance averaged across the 4 target directions. 95% CI (dotted black line) are also presented.

Smooth Pursuit Task

Smooth pursuit development of healthy controls was inspected based on 3 movement trajectories (horizontal, vertical, elliptical), which travelled at 2 different velocities (16 °/s and 6.5 °/s). Two measures were examined: the velocity gain of pursuit (*VeloGain*) and the frequency of forward saccades per second during pursuit (*ForwSacc*). First, AIC comparisons were conducted to test the 2-way interaction between *Conditon* and *Age* for *VeloGain* and *ForwSacc*. A model which included an interaction term was better than a model that did not for both *VeloGain* (test-model ΔAIC = 0; AIC*w* = .99; null-model ΔAIC = 621; AIC*w* < .01) and *ForwSacc* (test-model ΔAIC = 0; AIC*w* = .99; null-model ΔAIC = 306; AIC*w* < .01). To answer which pursuit conditions produced different developmental trajectories four models were defined and compared: A 1-term model with a single trajectory for all 6 pursuit conditions ('Combined' model), a 2-term model with separate trajectories for fast and slow target velocities ('Velocity' model), a 3-term model with separate trajectories for the 3 pursuit patterns ('Hori / Vert / Elip' model), and a 6-term model with a trajectory for each of the 6 pursuit conditions ('Separate' model). AIC comparisons are presented in Table 4.5.12.

Table 4.5.12: Healthy controls smooth pursuit task– AIC condition comparisons

VeloGain Model	ΔAIC	AIC*w*	Evidence ratio
Separate	0	.999	1
Hori / Vert / Elip	416	<.001	> 1000
Velocity	633	<.001	> 1000
Combined	637	<.001	> 1000
ForwSacc Model	ΔAIC	AIC*w*	Evidence ratio
Separate	0	.999	1
Velocity	214	<.001	> 1000
Hori / Vert / Elip	301	<.001	> 1000
Combined	307	<.001	> 1000

Inspection of the AIC of developmental trajectories (linear, quadratic, or plateau) for the velocity gain (*VeloGain*) is presented in Table 4.5.13. The analysis was based on the 'Separate' model (Table 4.5.12) so 6 developmental trajectories are compared. Due to the scale of *VeloGain* (ratio of eye-target velocity), age is expressed in years (instead of months) in order to produce meaningful model parameters.

Table 4.5.13: Healthy controls velocity gain– AIC trajectory comparisons

Linear Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates		Fit Summary
	Linear	Quadratic	Plateau	Intercept	Slope	R^2
Slow Hori	0 / .54	1.7 / .23	1.7 / .23	.753	.011	.24
Slow Vert	0 / .67	1.4 / .33	-	.844	.008	.12
Fast Hori	0 / .43	0.9 / .27	0.7 / .30	.725	.010	.22
Fast Elip	0 / .62	1.0 / .38	-	.692	.013	.38

Quadratic Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Linear Term	Quadratic Term	R^2
Slow Elip	2.1 / .25	0 / .75	-	.585	.002	.0003	.34
Fast Vert	4.2 / .11	0 / .89	-	.670	.001	.0004	.42

Development of *VeloGain* for four conditions (slow hori, slow vert, fast hori and fast elip) was best defined (ΔAIC = 0) by linear functions, and two conditions (slow elip and fast vert) were best defined by quadratic functions. Age explained over 20% of the observed variance in *VeloGain* for all pursuit conditions except 'slow vert'. For the 4 pursuit conditions best defined by linear functions (slow hori, slow vert, fast hori and fast elip), the relative likelihood of a quadratic function was nearly equivalent (ΔAIC < 2). While the

development of two pursuit conditions (slow elip and fast vert) was considerably more likely to have a quadratic function (ΔAIC > 2). These different function preferences were further explained by the developmental slopes shown in Figure 4.5.8. For the 2 conditions fitted with quadratic functions (fast vert and slow elip) the change in performance among younger participants (6 – 10 years) was minimal; it was only at older ages that age-related changes occurred, which explained the preference for quadratic models in these cases. In contrast, the change in performance across the age range for the 4 remaining conditions (slow hori, fast hori, slow vert and fast elip) occurred linearly.

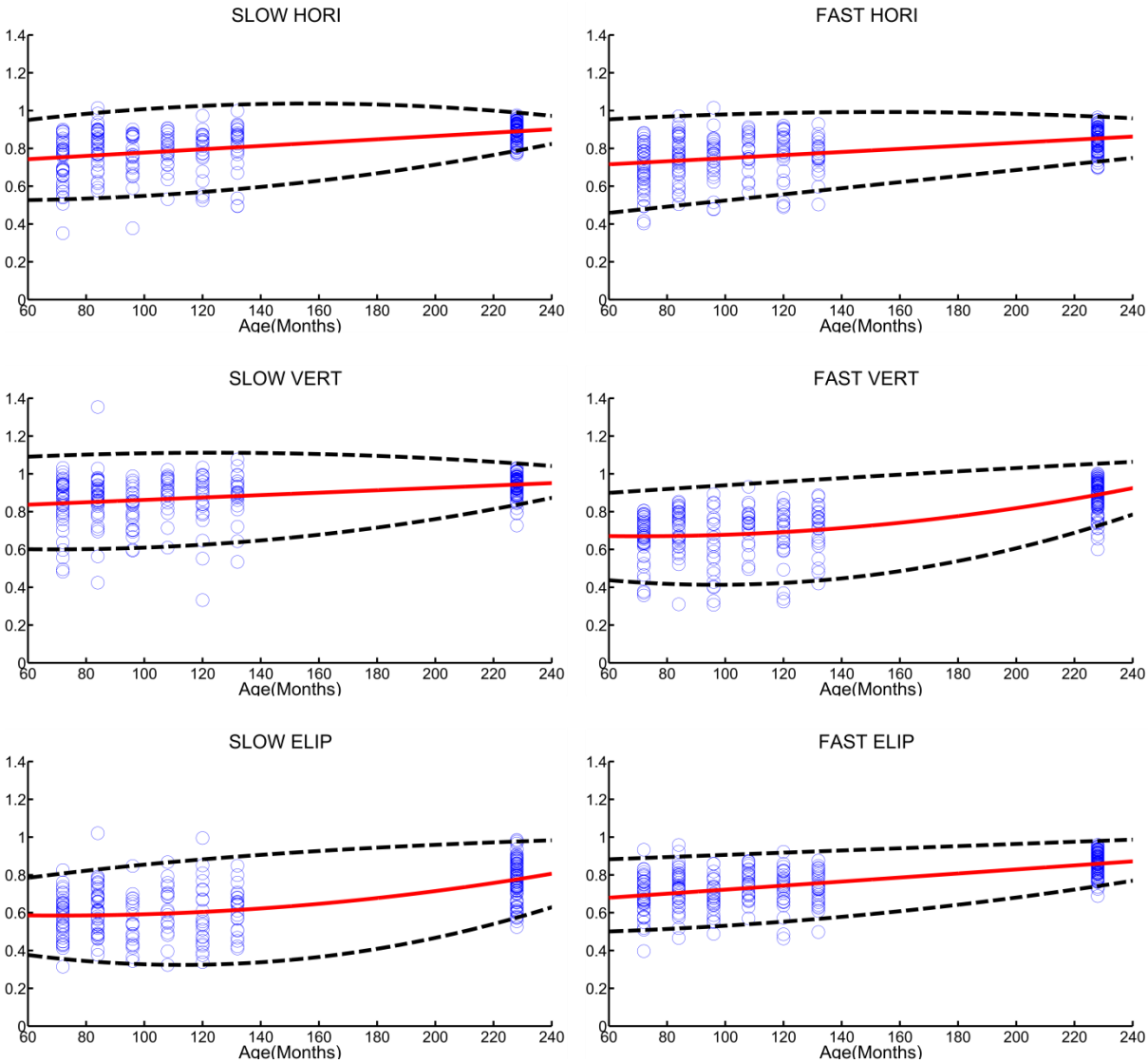


Figure 4.5.8: Healthy controls smooth pursuit velocity gain developmental trajectories. Mean velocity gain (*VeloGain*) of healthy developing controls (blue dots) during the smooth pursuit task. Most likely (ΔAIC = 0) developmental trajectories are shown as red lines. Velocity gain is presented for each of the 8 target locations. 95% CI (dotted black line) are also presented.

Finally, the model parameters (Table 4.5.13) and developmental curves (Figure 4.5.8) for each *VeloGain* trajectory demonstrate the necessity for condition-specific developmental trajectories. There was a large difference between the *VeloGain* intercepts of fast and slow velocities for vertical (slow = .844 ; fast = .670) and elliptical conditions (slow = .585 ; fast = .692). In contrast, the difference between the velocities of the horizontal condition was minimal (slow = .753 ; fast = .725). Interestingly, for vertical conditions *VeloGain* was

greater for slow velocities, while for elliptical conditions *VeloGain* was greater for fast velocities.

Inspection of the AIC of developmental trajectories (linear, quadratic, or plateau) for the frequency of forward saccades per second (*ForwSacc*) is presented in Table 4.5.14. The analysis is based on the 'Separate' model (Table 4.5.12) so 6 developmental trajectories are compared. Due to the scale of *ForwSacc* (range: 0 – 5), age is expressed in years (rather than months) for the definition of model parameters.

Table 4.5.14: Healthy controls forward saccade frequency– AIC trajectory comparisons

Linear Models

	AIC Results (ΔAIC / AICw)			Model Parameter Estimates		Fit Summary
	Linear	Quadratic	Plateau	Intercept	Slope	R^2
Slow Hori	0 / .69	1.6 / .32	-	1.62	-.017	.01
Fast Hori	0 / .63	1.0 / .37	-	2.63	-.059	.19
Fast Vert	0 / .51	2.0 / .19	1.0 / .30	2.14	-.005	<.01

Quadratic Models

	AIC Results (ΔAIC / AICw)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Linear Term	Quadratic Term	R^2
Fast Elip	3.4 / .15	0 / .85	-	2.09	-.010	.0003	<.01

Plateau Models

	AIC Results (ΔAIC / AICw)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Rate Constant	Plateau	R^2
Slow Vert	1.2 / .28	1.8 / .21	0 / .51	2.07	1.074	1.766	.03
Slow Elip	6.7 / .02	.82 / .39	0 / .59	1.98	.799	1.591	.05

Forward saccade development of three pursuit conditions (slow hori, fast hori and fast vert) was best described by linear functions, 2 conditions (slow vert and slow elip) were described best by plateau functions, and 1 condition (fast elip) was described best by a quadratic function. For 5 pursuit conditions, changes in age only explained a small proportion of *ForwSacc* variance ($R^2 < .051$). This suggests that little to no developmental change occurs within the age range of the sample for these conditions. For the remaining pursuit condition (fast hori), age explained 18% of the observed *ForwSacc* variance.The developmental slopes (Figure 4.5.9) further clarify these findings. *ForwSacc* performance on all (expect fast hori)

conditions remains relatively unchanged across of the different age groups. For the ‘fast hori’ condition younger participants (6 years) produce a larger number of saccades (2.633 saccades per second) in comparison to the other conditions, while the performance of older participants (19 years) is similar across conditions.

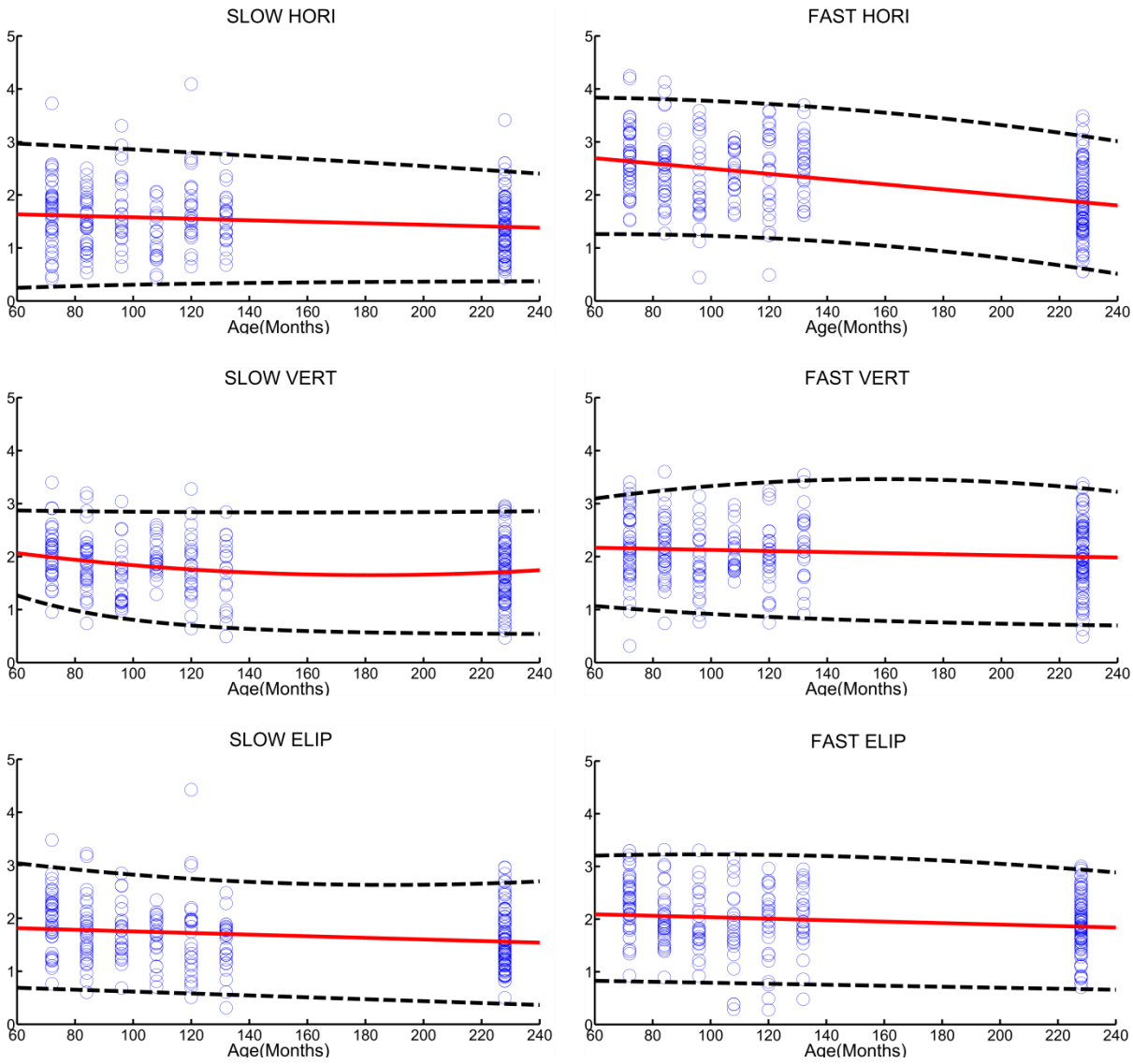


Figure 4.5.9: Healthy controls smooth pursuit forward saccade developmental trajectories. Mean frequency of forward saccades (*ForwSacc*) of healthy developing controls (blue dots) during the smooth pursuit task. Forward saccades are presented for each of the 6 target locations. 95% CI (dotted black line) are also presented.

4.6 Chapter Conclusions

In the current chapter a large sample of healthy developing participants were tested on measures of attention, language, and oculomotor function to define trajectories of normal cognitive development. To achieve this, AIC comparisons were conducted to identify the most likely descriptions of developmental change and to inspect the influence of experimental conditions. This is important as the following chapters of the thesis concern the comparison of rare metabolic patients to trajectories of healthy cognitive development. So having accurate representations of cognitive development is critical.

Attention was assessed using a simple reaction time and visual search task. Both tasks demonstrated clear developmental change with older participants producing faster response times on both tasks. For visual search, development trajectories were steeper and set-size effects were more prominent for conjunction in comparison to feature search. These findings are congruent with previous visual search research (Hommel et al., 2004b; Plude et al., 1994; Ruskin & Kaye, 1990; Trick & Enns, 1998), and is believed to reflect developmental differences between top-down attention (serial search – conjunction search) and bottom-up (parallel search – feature search) attentional processes (Duncan & Humphreys, 1989; Treisman & Gelade, 1980). In addition, on both task types it was found that developmental effects were greater for overall search time than for the efficiency of search. This suggests that the majority of developmental change was a reflection of improvements in processes related to decision time and response preparation. Developmental trajectories from both tasks will be used to identify attention deficits in metabolic patients.

Three tasks were used to assess children's language function: the British Picture Vocabulary Scale (BPVS; Dunn et al., 1997), the Boston Naming Task (BNT; Kaplan, 2000) and a novel non-word repetition task. The BPVS and BNT are standardised measures of receptive and productive vocabulary (respectively), and are commonly used to evaluate the

vocabulary proficiency of children. Unsurprisingly, developmental trajectories for these tasks were shown to be highly sensitive to changes in age. The non-word repetition task was a novel task designed to assess participants non-word learning proficiency in a supported learning context (Carey, 1978). The analysis revealed that older participants were able to recognise and produce more non-words than younger participants over the course of the learning phase. Developmental trajectories for receptive (BPVS) and productive (BNT) vocabulary, and non-word learning task will be used to identify language deficits in metabolic patients.

The oculomotor function of healthy developing controls was inspected using 4 tasks: a fixation task, pro-saccade task, anti-saccade task, and smooth pursuit task. For the fixation task, developmental change occurred rapidly between 6 – 10 years of age with development plateauing thereafter. This corresponded to an increase in total fixation time (*FixDwell*) and decrease in frequency of saccadic intrusions (*FixSacc*). Reflexive saccades, as measured by the pro-saccade task, revealed a decrease in initiation latency (*SaccOnset*) but no change in saccade velocity (*SaccVelo*) as a function of age. However despite the lack of developmental change found in saccade velocity, this measure will still be included in the following patient analysis due to saccadic velocity being affected in several neurodegenerative disorders (e.g. Niemann-Pick type C, Gaucher's Disease). For the anti-saccade task, participants demonstrated improved reflexive saccade suppression (*AntiErr*), improved self-error correction (*AntiCorr*), and decrease in anti-saccade target location latency (*AntiOffset*) as a function of age. However for the suppression of reflexive saccades, ceiling effects were present among younger participants (6 – 11 years) and the between-participant variance was substantial for older participants. This suggested that the difficulty of saccade suppression in the current paradigm was too high, which could be due to the requirement placed on participants to generate anti-saccades to a position based not only on direction but also

amplitude (inner / outer). Consequently, the difficulty of the anti-saccade task means the analysis of reflexive saccade suppression was removed from the patient analysis. Finally, for the smooth pursuit task healthy developing participants demonstrated reliable age related improvements for velocity gain (*VeloGain*). In contrast, the frequency of catch-up saccades (*ForwSacc*) was only sensitive to the pursuit condition where the target travelled vertically at a fast velocity.

5.0 LYSOSOMAL STORAGE DISORDERS

In this section of the thesis I will detail findings from three patient groups that are diagnosed with lysosomal storage disorders: Morquio syndrome (MPS-IVa), Hurler-Scheie syndrome (MPS-IH) and Maroteaux-Lamy syndrome (MPS-VI). In accordance with findings from previous research (refer to Chapter 2), each of these disorders has been shown to possess very different neuropsychological profiles. Intellectual functioning in Hurler-Scheie patients deteriorates as a function of disease progression (Elkin et al., 2006), Morquio patients can display mild cognitive deficits in working memory and full-scale IQ (Davison et al., 2012) while Maroteaux patients are believed to possess a normal cognitive profile (Neufeld & Muenzer, 2001; J Ed Wraith, 2006). While previous work typically relies on scores from standardised test batteries, I will report more detailed cognitive testing of visual attention, non-word learning, and oculomotor function.

The method for comparing patients to the healthy developmental trajectories defined in Chapter 4 will first be described. In general this includes the description of individual patient z-scores in comparison to healthy developing trajectories and the AIC comparison of patient and control developmental trajectories. Findings for each patient group will be presented separately with performance on each cognitive domain reported in turn. The current chapter intends to address two critical questions: first, is it possible to identify cognitive deficits in individual patients (z-scores) and, second, what is the likelihood (AIC comparison) that the development of these disorders differs to controls?

5.1 Data Analysis – Patient comparisons

Comparing individual patients to healthy controls

The performance of individual patients is expressed as z-scores. Each patient z-score is obtained through the comparison of the patient's performance to the healthy developmental trajectories defined in the previous chapter. This was accomplished by first acquiring residuals (Y_{resid}) for patients that were based on the comparison of patient performance (Y) to performance predictions (Y_{pred}) acquired from healthy developing trajectories (Figure 5.1.1). Equation 1 below was used to calculate residuals where task improvements occurred in a positive direction (i.e. improvements were associated with higher raw scores). Equation 2 was used to calculate residuals where task improvements were related to changes in a negative direction (i.e. improvements were associated with lower raw scores). This was to ensure that negative residual values always reflected patient performances that were below the predicted level across measures.

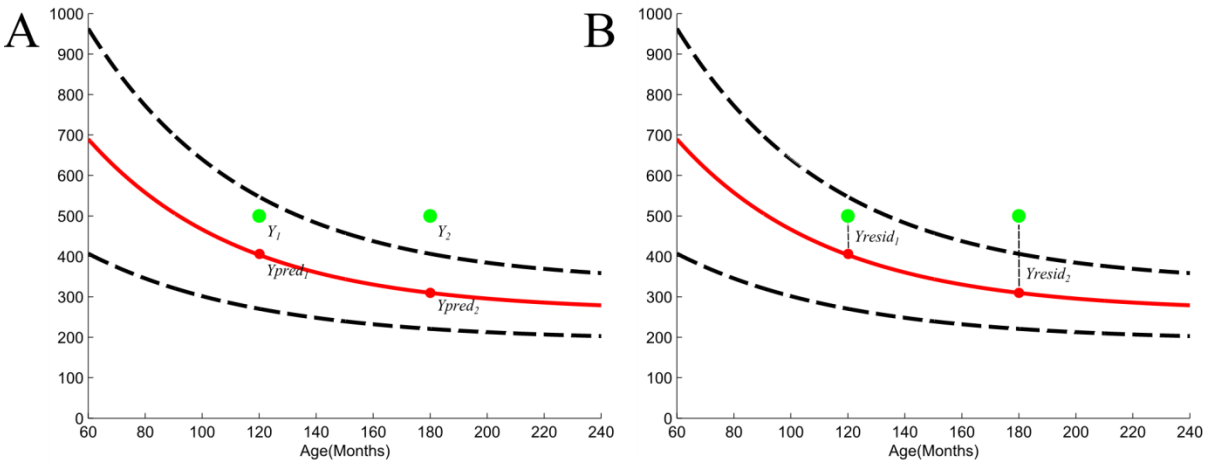


Figure 5.1.1: Patient residual calculations. Two fictitious patient scores (green points) for mean response time during the simple reaction time task. Panel A shows the raw scores (*Y*) of the two patients and their scores predicted (*Ypred*) from the healthy developing trajectory (red line). Panel B presents the residuals (*Yresid*; vertical black dashed-line) of the two patients that are computed from the *Y* and *Ypred* values. While both patients possess equal *Y* values (500ms), the *Yresid* values differ with the older patient having a larger *Yresid*.

1) $Y_{resid} = Y - Y_{pred}$

2) $Y_{resid} = Y_{pred} - Y$

Residuals were transformed into z-scores to identify where patients fell within the healthy developing distribution for their age. This process first required a variance calculation (Y_{SD}; Equation 3) that represented the relative estimated variance for the healthy sample at the patient's age. Using this Y_{SD} value it was then possible to calculate a patient's z-score (Y_Z; Equation 4).

3) $Y_{SD} = \frac{Y_{pred} - Y_{CI}}{1.96}$

4) $Y_Z = \frac{Y_{resid}}{Y_{SD}}$

A z-score of greater than ±1 means the patient is in a range that includes 84% of the control population. While a score of -1 means that the patient is worse than 84% of the control population, and a value of less than -2 means they are worse than 97.5% of the control population.

The above process can be illustrated using the example shown in Figure 5.1.1. Here two patients of differing ages (120 and 180 months) produce mean reaction times of 500ms (*Y*) during the simple reaction time task. While the reaction times are the same, the predicted values (Y_{pred}) are not. Leading to a greater negative residual for the older patient ($Y_{resid} = Y_{pred} - Y$ = 300 – 500 = -200) than the younger patient ($Y_{resid} = Y_{pred} - Y$ = 400 – 500 =

-100). Z-scores are then calculated to determine whether either patient fell outside the range of the healthy controls. The younger patient obtained a z-value of -1.307 (Y_Z = $\frac{Y_{resid}}{(Y_{CI-}\,Y_{pred})/1.96}$ = $\frac{-100}{(550-400)/1.96}$ = -1.307) that indicated their performance to be in the predicted lower average range of healthy developing controls. In contrast, the older patient produced a z-value of -3.920 (Y_Z = $\frac{Y_{resid}}{(Y_{CI-}\,Y_{pred})/1.96}$ = $\frac{-200}{(400-300)/1.96}$ = -3.920) that showed their performance to be clearly below the predicted range of healthy controls.

Comparing groups of patients to healthy developing controls

Model selection with AIC was used to determine the best way of describing differences in development between patients and healthy controls. We used an arbitrary cutoff ($N > 8$) to define when we were willing to start looking at developmental differences beyond the scores of individual patients, since the number of data points required to represent a group trajectory cannot be too small. The model selection utilised the same non-linear mixed effects methodology used for describing the condition-specific trajectories of healthy controls that was outlined in Chapter 4. To account for differences between patients and controls, an additional factor representing *Group* was included in the analysis of main effects and interactions. Confidence limits of patient development are defined by prediction bands. This is because the method used to define confidence limits for healthy controls requires a substantial number of participants.

5.2 5.2 Morquio Syndrome (MPS-IVa)

Morquio Syndrome (MPS-IVa) is a lysosomal disorder that is not typically linked to cognitive deficits. However, recent findings (Davison et al., 2012) have highlighted the possible presence of mild cognitive deficits in MPS-IVa. The authors argued that these deficits are due to the role of keratan sulphate and chondroitin-6-sulfate in the coordination of neuroaxonal connection formation during foetal and neonatal brain development (Miller et al., 1997).

It is predicted that MPS-IVa patients will demonstrate the same mild cognitive deficits for language comprehension that were described by Davison et al. (2012). In the same study, parents reported (via a behaviour checklist) that patients demonstrated difficulties with attention / concentration. Hence, it is expected that this observation may translate to deficits on tasks that contain attentional components (simple reaction time, visual search, and fixation tasks). This prediction is further supported by MRI findings (Davison et al., 2012) of frontal abnormalities in the form of enlarged CSF spaces and white matter signal abnormalities. Hence, frontal areas involved in visual search (FEF, orbitofrontal cortex, anterior cingulate) and sustained attention (DLPFC) may be affected.

Patients

Thirteen patients diagnosed with Morquio syndrome (8 male, 5 female; mean age: 9.59 years, range: 5.27 – 14.39 years) were recruited by a research nurse at the Birmingham Children's Hospital (demographics in Table 5.2.1). All patients were considered to have a severe phenotype of the disease; however, no patients had a presentation of corneal clouding. Patients completed the assessments over the course of one month during weekly hospital visits for enzyme replacement therapy. All assessments were conducted at the Wellcome Trust Clinical Research Facility at the Birmingham Children's Hospital. Consent for all

children was obtained from the children's parents prior to testing. One patient was removed from the analysis due to having a diagnosis of severe autism.

Table 5.2.1: MPS-IVa summary of patient demographics

PID	Gender	CA (Years)	BPVS MA (Years)	Linguistic Profile
1	M	5.27	4.02	BL – English / Pashto
2	F	6.44	5.00	BL – English / Pashto
3	F	6.48	5.07	BL – Pashto / English
4	M	7.77	8.02	BL – English / Pashto
5	F	9.33	8.07	BL – Pashto / English
6	F	9.79	10.08	ML – English
7	M	9.84	7.07	BL – Manderin / English
8	M	10.28	7.06	BL – Pashto / English
9	M	11.71	15.10	ML - English
10	M	11.78	7.10	ML - English
11	F	12.05	11.04	BL – English / Pashto
12	M	14.39	11.03	BL – English / Pashto

Note: ML, Monolingual, BL, Bilingual

Table 5.2.2 provides a summary of the measures where deficits were observed in the Morquio patients (MPS-IVa). Possible (*) and consistent deficits (**) were assigned to measures where a few or the majority of patients exhibited difficulties respectively. As predicted, patients displayed deficits on measures that contained attentional elements: simple reaction time task, visual search task, fixation task, and anti-saccade task. The performance of Morquio patients did not differ to healthy controls on several oculomotor tasks (pro-saccade task and smooth pursuit) or language tasks (BNT, non-word task).

Table 5.2.2: MPS-IVa summary of cognitive impairments across domains

Domain	Task		Measures
Attention	Simple RT Task	*	*RTmean*
	Visual Search Task	**	*VSmean*
Language	BNT	-	
	BPVS	*	
	Non-Word Task	-	
Ocular Motor	Fixation Task	**	*FixDwell, FixCount*
	Prosaccade Task	-	
	Antisaccade Task	*	*AntiCorr*
	Smooth Pursuit	-	

Note: *RTmean*, Mean Reaction Time; *VSmean*, Mean Visual Search Time; *FixDwell*, Fixation Duration Time; *FixCount*, Fixation Count; *AntiCorr*; Frequency of Error Correction; Forward Saccade Frequency
* Possible deficit, ** Consistent deficits

5.2.1 Attention

Attention task results were examined on an individual and group basis. No modifications were made to the test protocol in order for the patients to complete the assessment. MPS-IVa patients presented clear deficits on the visual search task and a possible deficit on the simple reaction time task for mean response time (*RTmean*) only.

Simple Reaction Time Task

Mean response time (*RTmean*) of MPS-IVa patients during the simple reaction time task is displayed in Figure 5.2.1. Individual paient responses that were greater than 3 SDs away from individual patient means were defined as outlier and removed. *RTmean* was normal (i.e. within the confidence limits of healthy development (dashed-black line)) for the majority of patients on all target locations. However, a trend existed where the *RTmean* of the group was shifted upward towards the lower average range of normal.

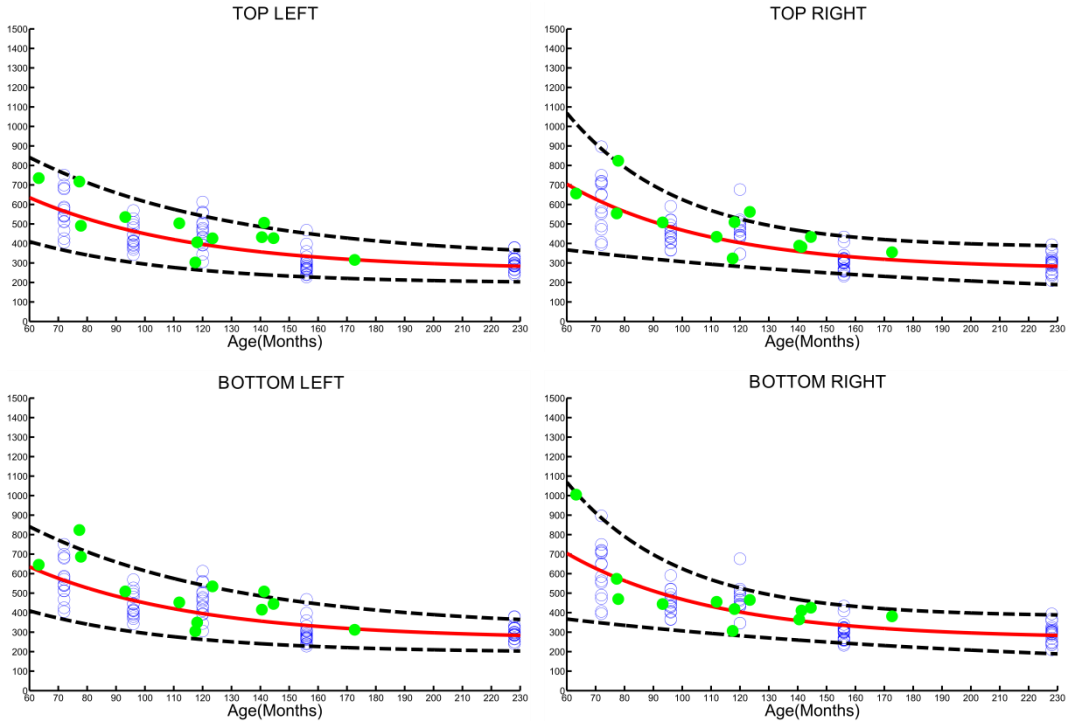


Figure 5.2.1: MPS-IVa simple reaction time indidual patient performance. Mean simple reaction time (*RTmean*) of MPS-IVa patients (green dots) and healthy developing controls (blue dots) in comparison to a healthy developmental trajectory (red line). The healthy control developmental trajectory is expressed as a quadratic function with 95% CI (dashed black line).

For specific target locations (Table 5.2.3), the frequency of patients producing extreme low response times (z-score > 2) was as follows: bottom-left (3/12 patients), bottom-right (0/12 patients), top-left (1/12 patients), top-right (2/12 patients). When performance was averaged across target locations, no patients exhibited extreme low response times (z-score > 2).

Table 5.2.3: MPS-IVa z-scores for simple reaction time (*RTmean*)

PID	Age (Years)	Bottom Left	Bottom Right	Top Left	Top Right	Avg
1	5.27	645 (-0.29)	1005 (-1.91) *	735 (-1.16) *	656 (0.14)	766 (-0.76)
2	6.44	823 (-2.96) **	573 (0.05)	717 (-1.86)	554 (0.21)	667 (-0.84)
3	6.48	687 (-1.57) *	470 (0.88)	491 (0.48)	824 (-2.03) **	618 (-0.43)
4	7.77	509 (-0.41)	444 (0.57)	535 (-0.71)	508 (-0.13)	499 (-0.06)
5	9.33	452 (-0.48)	455 (-0.42)	504 (-1.13) *	434 (-0.11)	461 (-0.45)
6	9.79	305 (1.39)	307 (1.62)	303 (1.43)	323 (1.36)	309 (1.45)
7	9.84	349 (0.73)	418 (-0.15)	406 (-0.08)	509 (-1.58) *	421 (-0.16)
8	10.28	535 (-2.02) **	465 (-1.16)	426 (-0.53)	562 (-2.75) **	499 (-1.47) *
9	11.71	415 (-0.90)	365 (-0.12)	432 (-1.16) *	389 (-0.55)	400 (-0.66)
10	11.78	508 (-2.35) **	411 (-0.98)	506 (-2.32) **	382 (-0.46)	449 (-1.48) *
11	12.05	445 (-1.48) *	425 (-1.36)	427 (-1.21) *	433 (-1.51) *	433 (-1.33) *
12	14.39	312 (0.09)	381 (-1.26)	316 (0.02)	355 (-0.75)	342 (-0.51)

Note: Reponses recorded in milliseconds, z-scores in parentheses
* *zscore > 1*, ** *zscore > 2*

To determine if the rate of development for simple response speed differed between MPS-IVa patients and controls, an AIC comparison was conducted to test the 2-way interaction between *Group* and *Age*. Here a model which included an interaction term (ΔAIC = 0 ; AIC*w* = .75) was slightly better than a model that did not (ΔAIC = 2.2 ; AIC*w* = .25). Thus, the overall rate of development of MPS-IVa patients and controls differed. Also, no specific target location influenced response time development differently between groups. This was shown in the lack of a 3-way interaction between *Group*, *TargetLocation* and *Age* (test-model (ΔAIC / AIC*w*) = 5.2 / .07 ; null-model (ΔAIC / AIC*w*) = 0 / .93). Finally, evidence for a main effect of *Group* (test-model (ΔAIC / AIC*w*) = 14 / <.01 ; null-model (ΔAIC / AIC*w*) = 0 / .99) and a 2-way interaction of *Group* and *TargetLocation* (test-model (ΔAIC / AIC*w*) = 2.7 / .21 ; null-model (ΔAIC / AIC*w*) = 0 / .79) was weak. Therefore, the response time of patients was not offset from the response time of controls. The developmental slopes of MPS-IVa patients and controls (Figure 5.2.2) elucidate the above findings. Here, the shape of the MPS-IVa developmental trajectory differed to controls. This is because MPS-IVa development was best defined by a plateau function (ΔAIC = 0; AIC*w* =

.796; $Y = (766 – 366)*\exp(-.032 * X) + 366$), when compared to linear (ΔAIC = 10.224; AIC*w* = .005) and quadratic functions (ΔAIC = 2.824; AIC*w* = .195), whereas the development of controls was best defined by a quadratic function. Based on these function differences, it is possible that at later ages (170 months and above) the response time latency of MPS-IVa patients will diverge from healthy development, becoming slower as a consequence. However, this observation should be interpreted with caution due to the small number of patient data points used to construct the patient trajectory

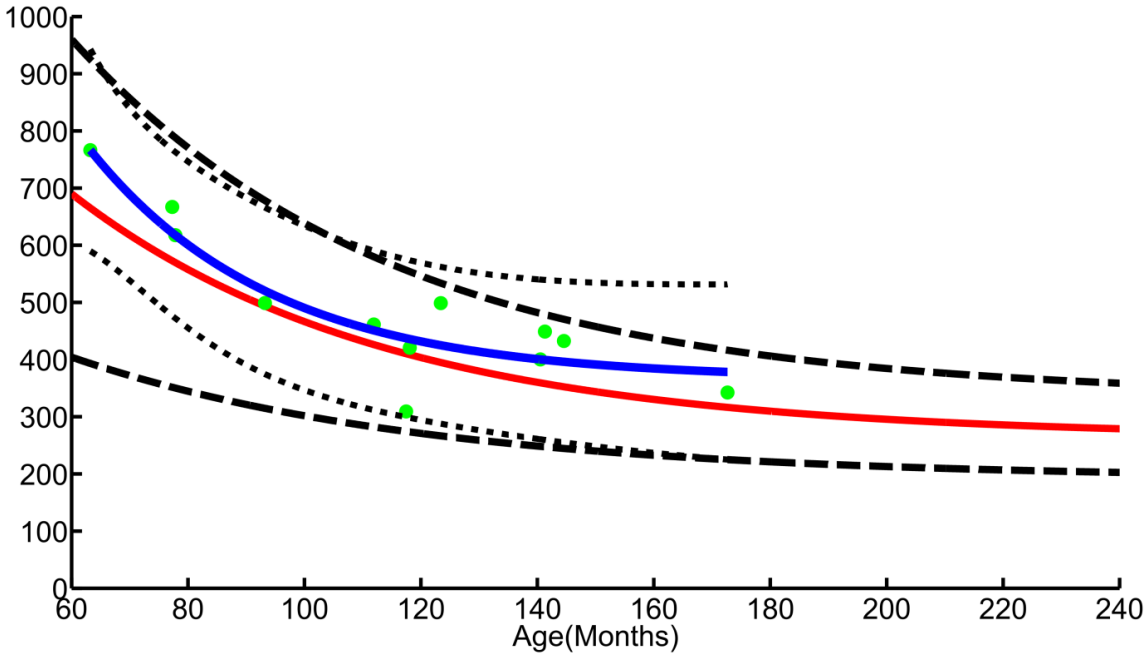


Figure 5.2.2: MPS-IVa simple reaction time developmental trajectories. Mean simple reaction time (*RTmean*) developmental trajectories of Morquio patients (blue line) and healthy developing controls (red line). Morquio patient raw scores presented as green dots. Reaction time is collapsed across target locations. The healthy developmental trajectory is expressed as a quadratic function with 95% CI (dashed black line) and Morquio developmental trajectory is expressed as a plateau function with 95% prediction bands (dotted black line).

Visual Search Task

Overall search time (*VSmean*) and search efficiency (*VSslope*; the search time required for each additional display item) of MPS-IVa patients on the visual search task is presented in Figure 5.2.3. Mean search time (*VSmean*) of patients was shifted towards the lower average range of healthy development for both feature and conjunction search.

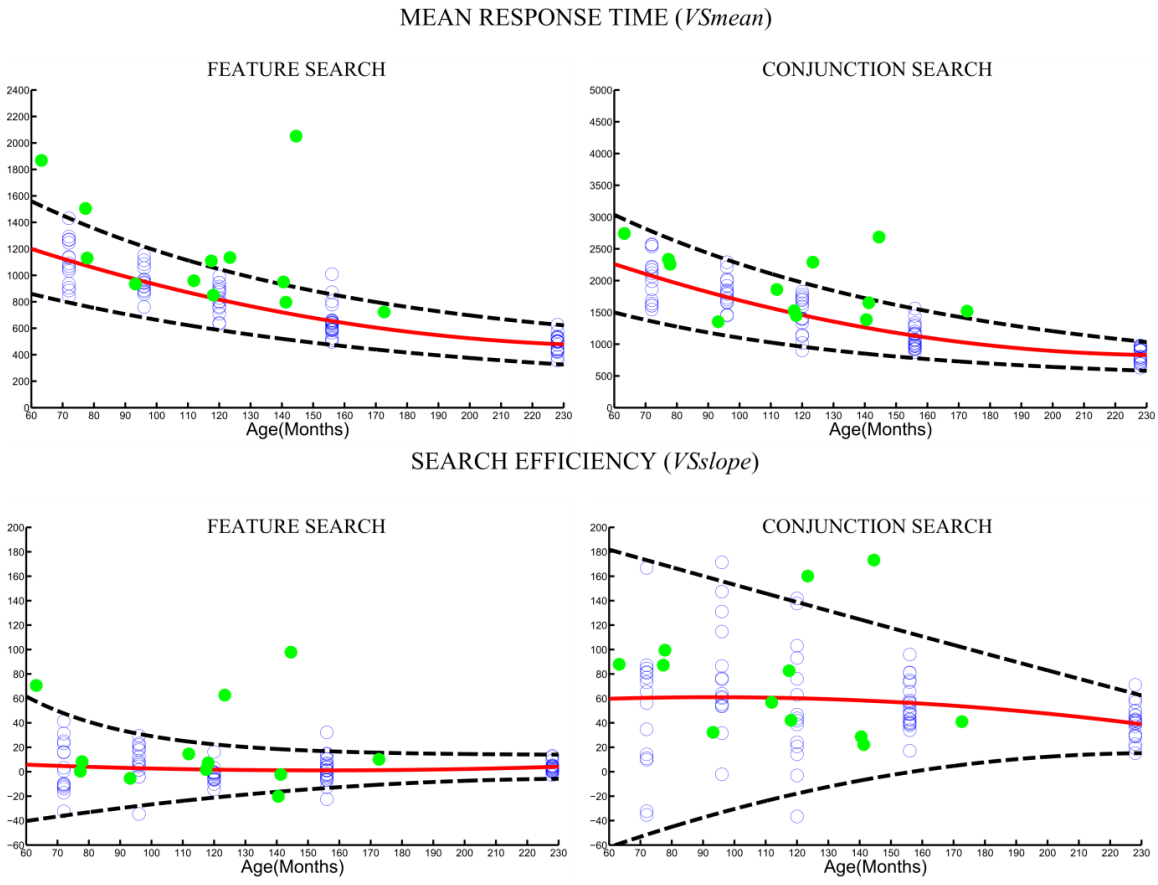


Figure 5.2.3: MPS-IVa visual search individual patient performance. Mean search time (*VSmean*) and search efficiency (*VSslope*) of MPS-IVa patients (green dots) and healthy developing controls (blue dots). Developmental trajectory of controls expressed as quadratic functions (red line) with 95% CI (dashed black line).

Table 5.2.4 displays the z-scores of individual MPS-IVa patients on the visual search task. For conjunction search, the efficiency of search (*VSslope*) of patient 8 (10.28 years : z-score = -2.57) and patient 11 (12.05 years : z-score = -3.55) was lower than controls. As a result, these patients also possessed slower mean conjunction search times (*VSmean*) than controls. Interestingly, the feature search efficiency of three patients was higher than controls. This included patient 1 (5.27 years : z-score = -2.46), patient 8 (10.28 years : z-score = -5.99) and patient 11 (12.05 years : z-score = -11.25). For the latter 2 patients (patient 8 and 11) feature search efficiency was drastically higher than controls, therefore, it is possible that parallel search mechanisms are not functioning correctly in these patients. Their conjunction search results may be a consequence of the effects on more basic search mechanisms.

Table 5.2.4: MPS-IVa z-scores for mean visual search times (*VSmean*)

PID	Age (Years)	Task	*VSmean*	*VSslope*
1	5.27	FS	1868 (-3.95) **	71 (-2.46) **
		CS	2742 (-1.37) *	88 (-0.46)
2	6.44	FS	1505 (-2.76) **	0 (0.20)
		CS	2336 (-1.00) *	87 (-0.48)
3	6.48	FS	1131 (-0.39)	8 (-0.21)
		CS	2257 (-0.80)	99 (-0.70)
4	7.77	FS	934 (0.22)	-5 (0.52)
		CS	1352 (1.32)	32 (0.59)
5	9.33	FS	959 (-0.83)	15 (-1.09) *
		CS	1860 (-1.16) *	57 (0.09)
6	9.79	FS	1109 (-2.34) **	2 (0.00)
		CS	1525 (-0.17)	83 (-0.54)
7	9.84	FS	850 (-0.22)	7 (-0.51)
		CS	1451 (0.09)	42 (0.45)
8	10.28	FS	1134 (-2.89) **	63 (-5.99) **
		CS	2290 (-3.38) **	160 (-2.57) **
9	11.71	FS	950 (-2.15) **	-20 (2.39) **
		CS	1385 (-0.50)	29 (0.89)
10	11.78	FS	797 (-0.74)	-2 (0.39)
		CS	1650 (-1.70) *	22 (1.09)
11	12.05	FS	2051 (-12.92) **	98 (-11.25) **
		CS	2685 (-6.53) **	173 (-3.55) **
12	14.39	FS	723 (-1.26) *	10 (-1.21) *
		CS	1519 (-2.58) **	41 (0.51)

Note: FS: Feature Search, CS: Conjunction Search, reponses recorded in milliseconds, z-scores in parentheses

** z-score > 1, ** z-score > 2*

Differences in visual search development between patients and healthy controls on feature and conjunction search were analysed separately. Patient 11 (12.05 years) was omitted from the trajectory analysis for having mean search times that were identified (Cook's distance) as clear outliers among MPS-IVa patients. For feature search, differences in search efficiency (*VSslope*) development were checked by examining the 3-way interaction for *Group*, *Setsize* and *Age*. A model that included an interaction term (ΔAIC = 1.7 ; AIC*w* = .299) was worse than a model without an interaction term (AIC*w* = .700). Therefore, the rate of feature search efficiency development of patients and healthy controls did not differ. In addition, there was a lack of a 2-way interaction model for *Group* and *Setsize* (test-model ΔAIC = 0.1 ; AIC*w* = .487 ; null model ΔAIC = 0 ; AIC*w* = .711). This means that the feature search efficiency of patients and controls (regardless of age) were also the same. However, a 2-way interaction for *Group* and *Age* indicated that the rate of feature search time (*VSmean*) development differed between groups (test-model (ΔAIC / AIC*w*) = 0 / .953 ; null-model (ΔAIC / AIC*w*) = 9.1 / .047). Finally, a main effect for *Group* (test-model (ΔAIC / AIC*w*) = 0 / .999 ; null-model (ΔAIC / AIC*w*) = 19.1 / .001) was found, indicating that feature search times, and the development of feature search times, were different between MPS-IVa patients and controls. Together, these results show that Morquio patients were slower overall but did not have a stronger effect of set size. This suggests that the difference between Morquio patients and controls is not due to mechanisms involved in processing search items sequentially, but instead, differences are likely to be due to factors that are constant across set-sizes, such as decision time.

The rate of conjunction search efficiency (*VSslope)* development did not differ between patients and controls. This was shown in the lack of a 3-way iteration for *Group*, *Setsize* and *Age* (test-model (ΔAIC / AIC*w*) = 1.2 / .279 ; null-model (ΔAIC / AIC*w*) = 0 / .721). In addition, the lack of a 2-way interaction for *Group* and *Setsize* (test-model (ΔAIC /

AIC*w*) = 1.8 / .289 ; null-model (ΔAIC / AIC*w*) = 0 / .711) indicated that the overall conjunction search efficiency of patients and controls did not differ. Finally, the mean conjunction search time (*VSmean*) of patients and controls did differ. This was demonstrated by a clear main effect for *Group* (test-model (ΔAIC / AIC*w*) = 0 / .973 ; null-model (ΔAIC / AIC*w*) = 7.2 / .026). However, the rate in which mean conjunction search time developed did not differ between groups (*Group* x *Age* = interaction-model (ΔAIC / AIC*w*) = .1 / .487 ; null-model (ΔAIC / AIC*w*) = 0 / .512). Similar to feature search findings, differences between patients and controls were due factors that were constant across set sizes, rather than mechanisms involved in serial search.

The fit of the MPS-IVa developmental trajectories to linear, quadratic or plateau functions was conducted to find the best description of MPS-IVa visual search development, and to answer how patient development differed to controls. Since differences between patients and controls were found for search time (*VSmean*), and not search slopes (*VSslope*), only the MPS-IVa developmental trajectories for feature and conjunction search times were defined. Results (Table 5.2.5) revealed that plateau functions offered the best description of MPS-IVa visual search development for both feature and conjunction search tasks.

Table 5.2.5: MPS-IVa visual search task: AIC trajectory comparisons

Plateau Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Rate Constant	Plateau	R^2
VSmean - FS	5.4 / .06	4.5 / .09	0 / .85	1864	.058	888	.77
VSmean - CS	2.1 / .20	1.7 / .24	0 / .56	2797	.053	1587	.53

Notes: FS: Feature Search, CS: Conjunction Search, reponses recorded in milliseconds

Developmental trajectory slopes of MPS-IVa patients and controls are in presented Figure 5.2.4. The slopes illustrate the search time differences that were identified between the groups. Firstly, for both feature and conjunction search, differences were evident at the youngest age of measurement. Compared to controls, MPS-IVa patients produced slower feature search (MPS-IVa = 1864ms ; Controls = 1132ms) and conjunction search responses (MPS-IVa = 2797ms ; Controls = 2074ms). However, this should be interpreted with caution since only a few patient data points occupy this region of development. Also, similar to simple response time latency, it is possible that the development of MPS-IVa patients may diverge from healthy controls during later ages, with patients becoming slower than healthy controls. This is due to the difference in the functions which characterise the development of patients (plateau function) and healthy controls (quadratic function). Therefore, compared to MPS-IVa patients, developmental change occurs over a longer time course in healthy controls. However, this should be interpreted with caution also as there are no older patient data points (180 – 240 months) to confirm this conclusion.

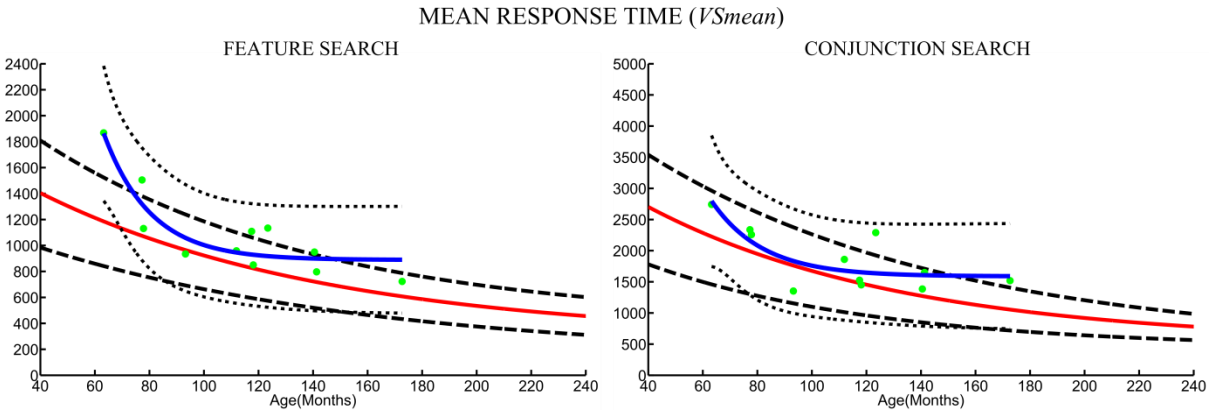


Figure 5.2.4: MPS-IVa visual search developmental trajectories. Mean search time (*VSmean*) developmental trajectories of MPS-IVa patients (blue line) and healthy developing controls (red line). MPS-IVa patient raw scores presented as green dots. The healthy developmental trajectories are expressed as a quadratic function with 95% CI (dashed black line) for all conditions. MPS-IVa development is expressed by plateau functions with 95% prediction bands (dotted black line).

5.2.2 Language

All MPS-IVa patients completed the *BPVS* task during their assessments, except for patient 12 who did not complete the *BNT* due to time constraints. For the non-word learning task, patient 7 was unable to complete the task, also due to time constraints.

MPS-IVa patients displayed minor difficulties on the *BPVS* task but did not differ to healthy controls on either the *BNT* or the non-word learning task. Consequently, language results for the *BPVS* are presented here along with *BNT* (as a comparison). Non-word learning results are not reported.

Production and Comprehension

Patient verbal production scores (*BNT*) and verbal comprehension scores (*BPVS*) are presented in Figure 5.2.5. Patient *BNT* scores were evenly distributed across the predicted mean of healthy development (red line). Patient *BPVS* scores fell within the normal range of development. However, many patients were shifted downwards towards the lower range of development.

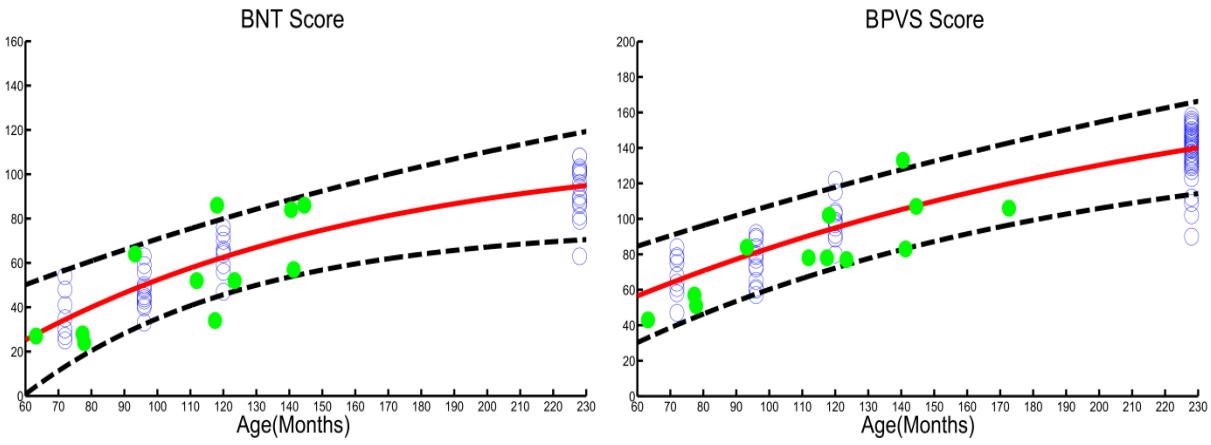


Figure 5.2.5: MPS-IVa verbal production and comprehension individual patient scores. Patient (green dots) and healthy control (blue dots) raw scores on the Boston Naming task (BNT, left) and the British Picture Vocabulary Scale (BPVS, right). Healthy developing trajectories (red line) are expressed as quadratic functions for both BNT and BPVS. 95% confidence limits are included (black dotted-line).

The individual patient *BNT* z-scores (Table 5.2.6) show that patient 6 (9.79 years) had a *BNT* score that was below the confidence limits (z-score = -3.17) while patient 7 (9.85 years) had a *BNT* score that was above the confidence limits (z-score = 2.74). The *BPVS* comprehension scores displayed in Table 5.2.6 show that no patients were outside the confidence limits of development (z-score > -2), however, 7/12 patients were in the lower average (z-score > -1).

Table 5.2.6: MPS-IVa z-scores for verbal production and comprehension

PID	Age (Years)	Boston Score	BPVS Score
1	5.27	27 (-0.07)	43 (-1.20) *
2	6.44	28 (-0.99)	57 (-0.94)
3	6.48	24 (-1.42) *	51 (-1.45) *
4	7.77	64 (1.60)	84 (0.38)
5	9.33	52 (-0.77)	78 (-1.06) *
6	9.79	34 (-3.17) **	78 (-1.34) *
7	9.84	86 (2.74)	102 (0.69)
8	10.28	52 (-1.40) *	77 (-1.71) *
9	11.71	84 (1.44)	133 (2.40)
10	11.78	57 (-1.63) *	83 (-1.98) *
11	12.05	86 (1.48)	107 (-0.03)
12	14.39		106 (-1.16) *

* *z-score > 1, ** z-score > 2*

To inspect differences in the development rate of verbal comprehension of MPS-IVa patients and controls, an AIC comparison was conducted to test the presence of a 2-way interaction between *Group* and *Age*. Here a model which included an interaction term (ΔAIC = 0; AIC*w* = .817) was better than a model that did not (ΔAIC = 3 ; AIC*w* = .182) However, a main effect of *Group* was not found (test-model (ΔAIC / AIC*w*) = .1 / .487 ; null-model (ΔAIC / AIC*w*) = 0 / .512). This means that only the rate development between patients and controls differed.

The development of verbal comprehension for MPS-IVa patients was best defined by a linear function ($Y = 49.5 + .65 * X$; ΔAIC = 0; AICw = .438) rather than a quadratic (ΔAIC = .83 ; AICw = .288) or plateau functions (ΔAIC = .95; AICw = .273). Figure 5.2.6 illustrates the findings from the above analysis. In general, the overall performance of patients did not differ to the performance of controls; all patient data points are distributed within the range of healthy development. This is reflected in the lack of a main effect for *Group*. However, MPS-IVa patients demonstrated a steeper developmental slope than controls, which means patient performance may convergence with heathly control performance during later years.

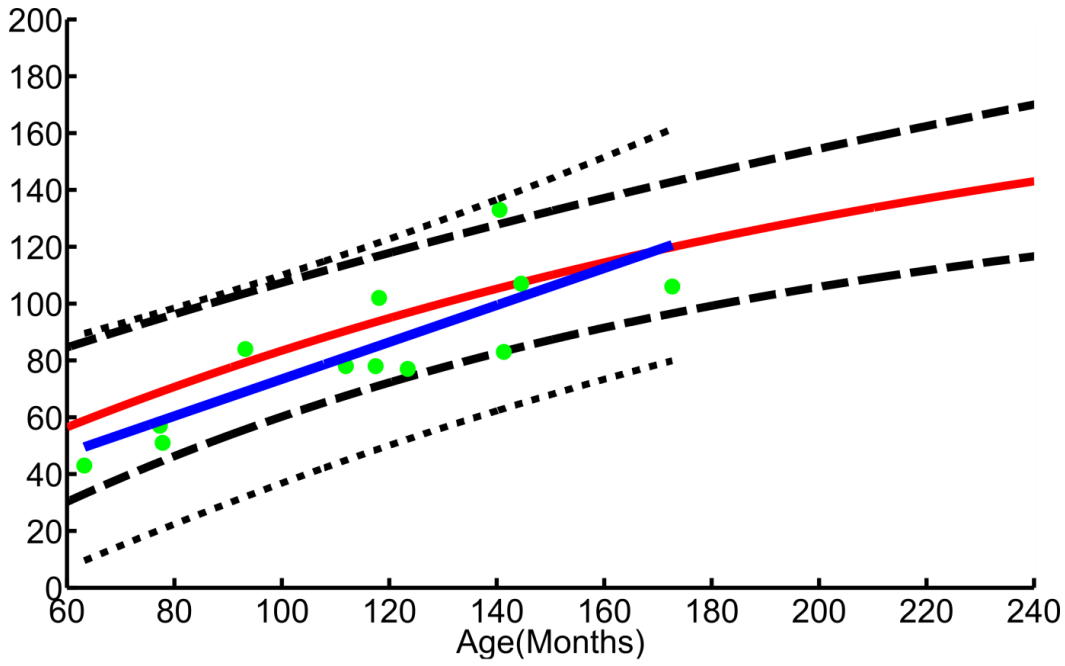


Figure 5.2.6: MPS-IVa verbal comprehension developmental trajectory. BPVS developmental trajectories of MPS-IVa patients (blue line) and healthy developing controls (red line). MPS-IVa patient raw scores presented as green dots. The healthy developmental trajectory is expressed as a quadratic function with 95% CI (dashed black line) and MPS-IVa developmental trajectory is expressed as a linear function with 95% prediction bands (dotted black line).

5.2.3 Oculomotor

Eleven of the 12 Morquio patients completed the fixation task. The youngest patient was unable to complete the task due to being highly inattentive during the testing session and was unable to be calibrated. Patients 5 and 7 could only complete the fixation task due to irritability and patients 2, 3, 4 and 11 could not complete the anti-saccade and smooth pursuit task due to fatigue.

Results from the fixation task and anti-saccade task are presented only. No patients exhibited impairments on the pro-saccade and smooth pursuit tasks. Fixation task performance will be described on an individual and group basis. Anti-saccade task performance will be described on an individual basis only due to the smaller sample size.

Fixation Task

The average fixation duration (*FixDwell*) of MPS-IVs patients is presented in Figure 5.2.7. For the left, right, and bottom target locations the majority of patients exhibited fixation durations that were clearly outside the confidence limits of healthy development. These fixation deficits were present in both younger and older patients. Fewer patients appeared to produce clear deficits for the top target location. However, even in this condition all patients were below the predicted mean of development (red line).

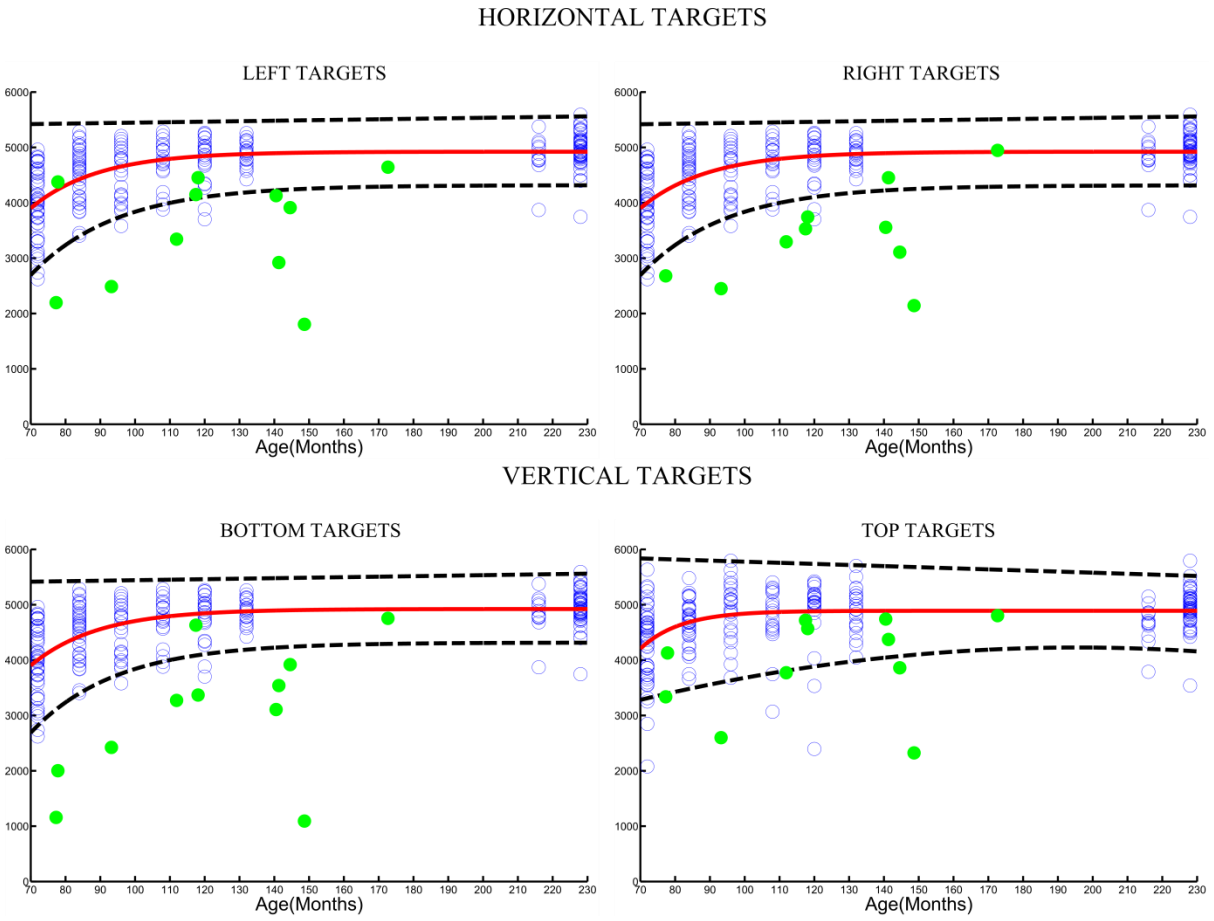


Figure 5.2.7: MPS-IVa fixation duration individual patient performance. Average fixation duration (*FixDwell*; ms) for MPS-IVa patients (green dots) and healthy controls (blue dots). Horizontal target locations are shown in the top row of graphs and vertical target locations are shown in the bottom row of graphs. The healthy developmental trajectory (red line) is expressed as a plateau function. 95% confidence limits (black dotted-line) are presented.

Table 5.2.7 displays the *FixDwell* z-scores of individual patients. When *FixDwell* was averaged across the 4 target locations, 8/11 patients exhibited clear fixation duration deficits (z-score > 2). Five of these 8 patients presented very clear deficits (z-score > 3), while patient 11 (12.39 years) displayed extremely low fixation durations (z-score = -9.22).

Table 5.2.7: MPS-IVa z-score for mean fixation duration (*FixDwell*)

PID	Age (Years)	Target Position				Avg
		Left	*Right*	*Bottom*	*Top*	
2	6.44	2197 (-3.57) **	2680 (-2.72) **	1158 (-5.39) **	3337 (-2.05) **	2343 (-3.59) **
3	6.48	4377 (0.23)	4243 (0.23)	2002 (-3.97) **	4129 (-0.71)	3502 (-1.49) *
4	7.77	2487 (-4.49) **	2449 (-4.57) **	2423 (-4.63) **	2599 (-3.59) **	2478 (-4.76) **
5	9.33	3343 (-3.66) **	3295 (-3.78) **	3272 (-3.85) **	3771 (-2.03) **	3458 (-3.49) **
6	9.79	4148 (-1.79) *	3531 (-3.39) **	4631 (-0.53)	4719 (-0.31)	4257 (-1.56) *
7	9.84	4453 (-1.00) *	3744 (-2.86) **	3369 (-3.85) **	4569 (-0.60)	3957 (-2.38) **
8	11.71	4129 (-2.24) **	3556 (-3.91) **	3107 (-5.24) **	4741 (-0.34)	3883 (-2.99) **
9	11.78	2921 (-5.79) **	4453 (-1.30) *	3540 (-3.98) **	4373 (-1.21) *	3743 (-3.42) **
10	12.05	3912 (-2.93) **	3108 (-5.30) **	3918 (-2.91) **	3861 (-2.46) **	3700 (-3.59) **
11	12.39	1805 (-9.30) **	2143 (-8.26) **	1092 (-11.44)**	2324 (-6.33) **	1841 (-9.22) **
12	14.39	4643 (-0.86)	4946 (0.09)	4754 (-0.51)	4803 (-0.25)	4786 (-0.43)

Note: MS, Milliseconds; * *z-score > 1, ** z-score > 2*

The average frequency of intrusive saccades during fixations (*FixSacc*¸ i.e. the number of saccades made away from the target) produced by MPS-IVa patients is presented in Figure 5.2.8. For all target locations the majority of patients exhibited a higher number of intrusive saccades than expected.

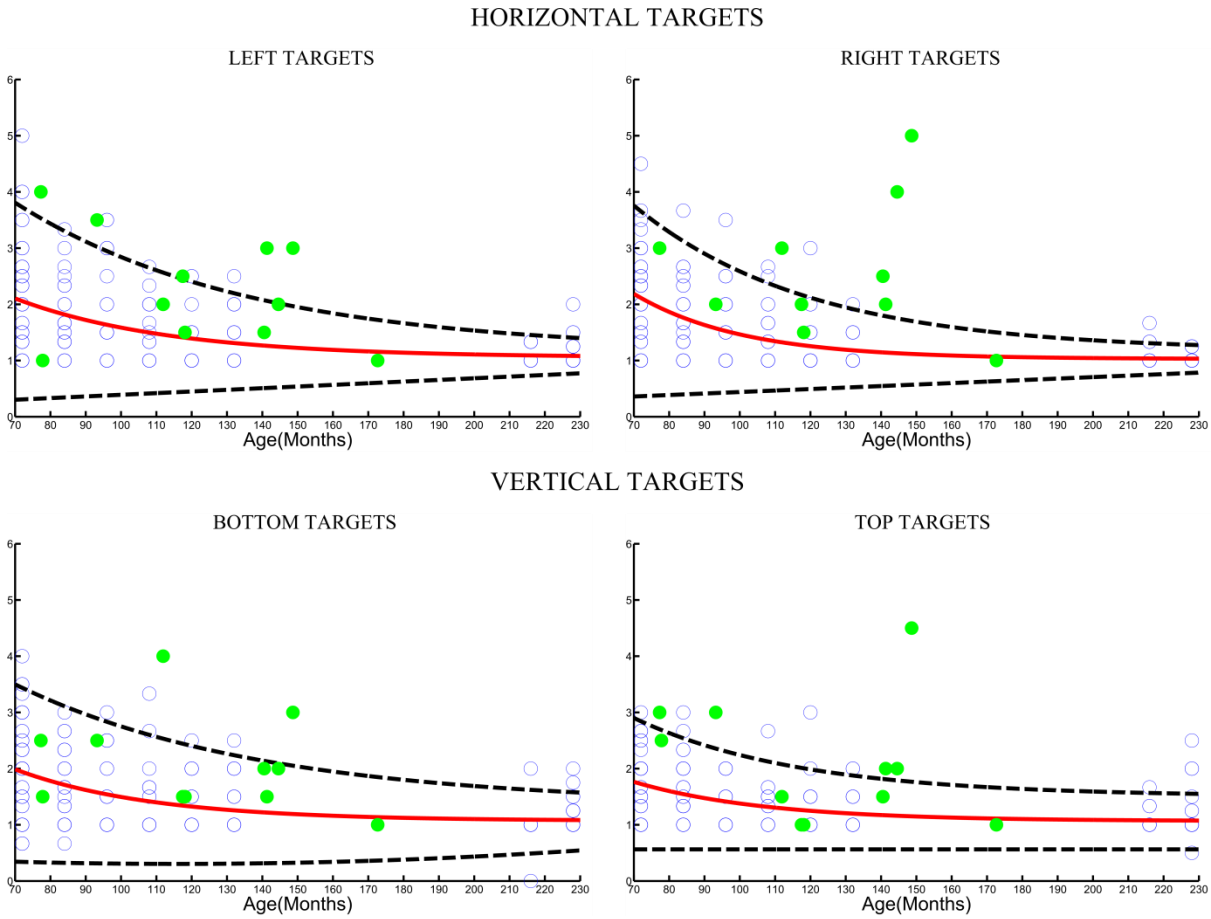


Figure 5.2.8:MPS-IVa intrusive saccade individual patient performance. Average number of saccades away from the visual stimulus (*FixSacc*) produced by Morquio patients (green dots) and healthy controls (blue dots). Horizontal target locations are shown in the top row of graphs and vertical target locations are shown in the bottom row of graphs. The healthy developmental trajectory (red line) is expressed as a plateau function. 95% confidence limits (black dotted-line) are also presented.

Results in **Table 5.2.8** display the *FixSacc* performance of MPS-IVa patients averaged across target locations. Here 7/11 patients produced a greater number of intrusive saccades than would be predicted for healthy development (z-score > 2). In addition, the age

of the patients who produced an abnormal number of intrusive saccades covered the age range of patients; abnormal performance was not exclusive to the youngest or oldest patients. Interestingly, these 7 patients also produced fixation duration (*FixDwell*) deficits, which suggest the difficulties with fixation maintenance are likely to be driven by problems suppressing intrusive saccades. One exception was patient 7 (9.84 years), who was within the normal healthy developing range for *FixSacc* but not *FixDwell*. Therefore it is unlikely that fixation maintenance deficits in Morquio syndrome are caused solely by difficulties suppressing saccades.

Table 5.2.8: MPS-IVa z-score for mean intrusive saccade frequency (*FixSacc*)

PID	Age (Years)	Target Position				*Avg*
		Left	*Right*	*Bottom*	*Top*	
2	6.44	4 (-2.54) **	3 (-1.42) *	3 (-0.90)	3 (-2.52) **	3 (-2.44) **
3	6.48	1 (1.14)	-	2 (0.42)	3 (-1.61) *	2 (0.29)
4	7.77	4 (-2.65) **	2 (-0.69)	3 (-1.37) *	3 (-3.34) **	3 (-2.71) **
5	9.33	2 (-0.96)	3 (-3.42) **	4 (-4.46) **	2 (-0.52)	2 (-3.04) **
6	9.79	3 (-2.05) **	2 (-1.59) *	2 (-0.28)	1 (0.73)	2 (-1.31) *
7	9.84	2 (-0.18)	2 (-0.51)	2 (-0.29)	1 (0.73)	1 (-0.35)
8	11.71	2 (-0.57)	3 (-4.06) **	2 (-1.67) *	2 (-1.00) *	2 (-2.70) **
9	11.78	3 (-4.26) **	2 (-2.60) **	2 (-0.61)	2 (-2.54) **	2 (-3.74) **
10	12.05	2 (-1.91) *	4 (-9.08) **	2 (-1.75) *	2 (-2.62) **	3 (-5.48) **
11	12.39	3 (-4.71) **	5 (-12.97) **	3 (-4.12) **	5 (-10.68) **	4 (-11.78) **
12	14.39	1 (0.55)	1 (0.31)	1 (0.34)	1 (0.40)	1 (0.67)

Note: MS, Milliseconds;
* *z-score > 1*, ** *z-score > 2*

Performance of patient 7 and 11 (along with age-matched controls) on the fixation task are shown in Figure 5.2.9. The temporal data of eye movements presented here illustrates the fixation deficits reported in these patients.

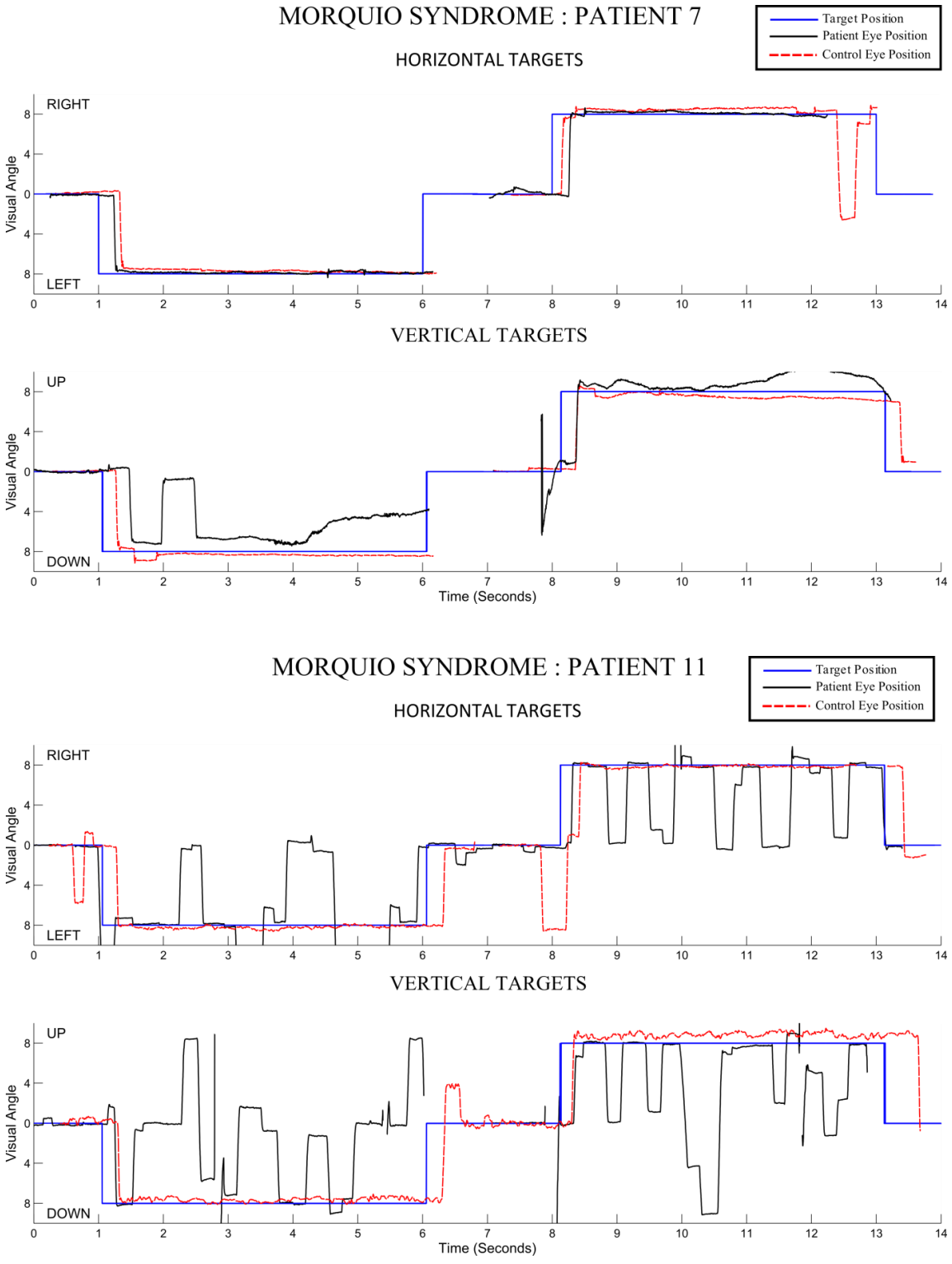


Figure 5.2.9: MPS-IVa fixation task raw temporal data. Eye movements of patient 7 and 11 during the fixation task. Both patients showed fixation duration deficits *(FixDwell*), while only patient 11displayed saccade frequency deficits (*FixCount*). The visual stimulus (blue line) is presented along with eye position of the patients (black line) and age-matched healthy controls (red dashed line). Horizontal and vertical eye movements are presented in the top and bottom panels respectively.

Patient 7 (9.84 years) displayed a fixation duration deficit (z-score = -2.38) but not a saccade frequency deficit (z-score = -0.35). The eye movements of patient 7 shown in Figure 5.2.9 demonstrate that this is due to disengagement from right and bottom presented targets near to the end of trials (disengagement from a bottom target is illustrated above). In contrast, patient 11 (12.39 years) presented with both a fixation duration (z-score = -9.22) and saccade frequency deficit (z-score = -11.78). Figure 5.2.9 highlights that both deficits are clearly due to the frequency of saccades during the task. A notable feature of patient 11's eye movements is that the patient continually shifts their gaze between the target and the screen centre.

The comparison of MPS-IVa and healthy developmental trajectories during the fixation task was examined through the comparison of AIC model values. First, to determine whether the overall rate of development (regardless of target location) for sustained fixation duration differed between patients and controls, an AIC comparison was conducted. There was insufficient evidence for a 3-way interaction of *Group*, *TargetLocation* and *Age* (test-model (ΔAIC / AIC*w*) = 1 / .38 ; null-model (ΔAIC / AIC*w*) = 0 / .62), but there was evidence of a 2-way interaction between *Group* and *Age* (test-model (ΔAIC / AIC*w*) = 0 / .73 ; null-model (ΔAIC / AIC*w*) = 2 / .27). Together, these results suggest that while patients and controls exhibit slightly different rates of development, the influence of target location on developmental change was the same for patients and controls. In terms of overall developmental differences between patients and controls, there was substantial evidence for a main effect of *Group* (test-model (ΔAIC / AIC*w*) = 0 / .99 ; null-model (ΔAIC / AIC*w*) = 11 / <.01) and an interaction of *Group* and *Targetlocation* (test-model (ΔAIC / AIC*w*) = 0 / .98 ; null-model (ΔAIC / AIC*w*) = 9 /.02). This means that overall developmental differences existed between groups and this difference varied across the four target locations. To identify whether overall developmental differences were systematically grouped, the AIC of the following 6 models were compared. A 1-term model with a single trajectory representing all

target locations ('Combined' model), a 2-term model with separate trajectories for horizontal and vertical targets ('Hori/Vert' model), and four 2-term models which each specified a separate trajectory for the four targets ('Left','Right','Top','Bottom' models). The ΔAIC values of each model are presented in Table 5.2.9. Here, the 'Top' model was the best model (ΔAIC / AIC*w* = 0 / .87). This means that the magnitude of the difference between patients and controls was not the same for top target location in comparison to the other target locations.

Table 5.2.9: MPS-IVa mean fixation duration (*FixDwell*) – AIC condition comparisons

Fix*Dwell* Model	ΔAIC	AIC*w*	Evidence ratio
Top	0	.87	1
Left	6	.04	20
Right	6	.04	20
Bottom	6	.04	20
Hori/Vert	15	<.01	>1000
Combined	32	<.01	>1000

Since the developmental onset differences between patients and controls were uniform across left, right, and bottom targets, the fit of the MPS-IVa developmental trajectories to linear, quadratic or plateau functions was analysed separately for the top target location. A separate developmental trajectory was defined for fixation duration based on the combined performance on left, right, and bottom targets ('L / R / B' development). Results revealed linear functions to clearly offer the best description of development for both the top target and the remaining targets locations (Table 5.2.10). Intercept parameter estimates, and the developmental slopes of MPS-IVa patients and controls (Figure 5.2.10), show that the difference between groups was smaller for the top target location (MPS-IVa = 3572ms ;

controls = 4319ms) in comparison to the other targets (MPS-IVa = 2664ms ; controls = 4001ms). In all locations, the Morquio patients were showing gradual improvement at an age where controls had plateaued.

Table 5.2.10: MPS-IVa mean fixation duration (*FixDwell*) – AIC trajectory comparisons

Linear Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates		Fit Summary
	Linear	Quadratic	Plateau	Intercept	Slope	R^2
Top	0 / .61	2.3 / .19	2.3 / .19	3572	96	.08
L / R / B	0 / .76	2.3 / .24	-	2664	169	.22

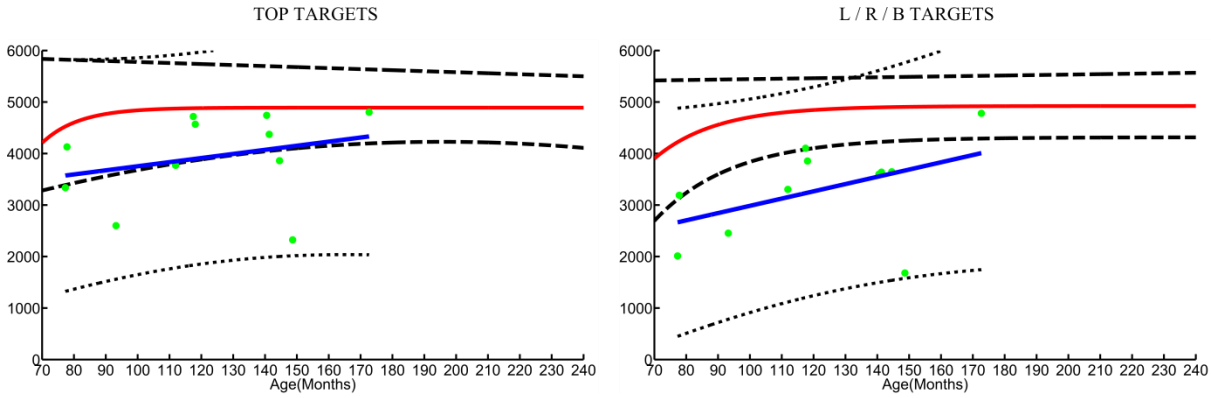


Figure 5.2.10: MPS-IVa fixation duration developmental trajectories. Mean fixation duration (*FixDwell*) developmental trajectories of MPS-IVa patients (blue line) and healthy developing controls (red line). MPS-IVa patient raw scores presented as green dots. The healthy developmental trajectory is expressed as a plateau function with 95% CI (dashed black line) and Morquio developmental trajectory is expressed as a linear function with 95% prediction bands (dotted black line).

The comparison of MPS-IVa and healthy developmental trajectories for the frequency of intrusive saccades (*FixSacc*) was examined with the same AIC model comparison procedure. Here, AIC comparisons for 2- and 3- way interactions, and main effects, provided

insufficient evidence of effects of group, target location and age. Therefore, the rate of development for intrusive saccades did not differ between MPS-IVa and healthy controls.

Pro-saccade Task

The reflexive saccade properties (saccade initiation latency (*SaccOnset*) and saccade velocity (*SaccVelo*)) were within range of normal healthy controls for all Morquio Patients. Consequentially these results are not presented here.

Anti-saccade Task

Five MPS-IVa patients completed the anti-saccade task. Seven patients did not complete the task due to irritability which prevented adequate calibration of the eye tracker. The time taken to locate the anti-saccade target (*AntiOffset*) was within the normal range of healthy development for the 5 patients. However, the proportion of corrected errors (*AntiCorr*) of several patients was below the lower limit range of healthy controls. The proportion of corrected anti-saccade errors (*AntiCorr*) of individual MPS-IVa patients is presented in Figure 5.2.11. In terms of deficits for specific target locations, no discernible pattern was observed; deficits were not more common for inner versus outer targets, or horizontal versus vertical targets.

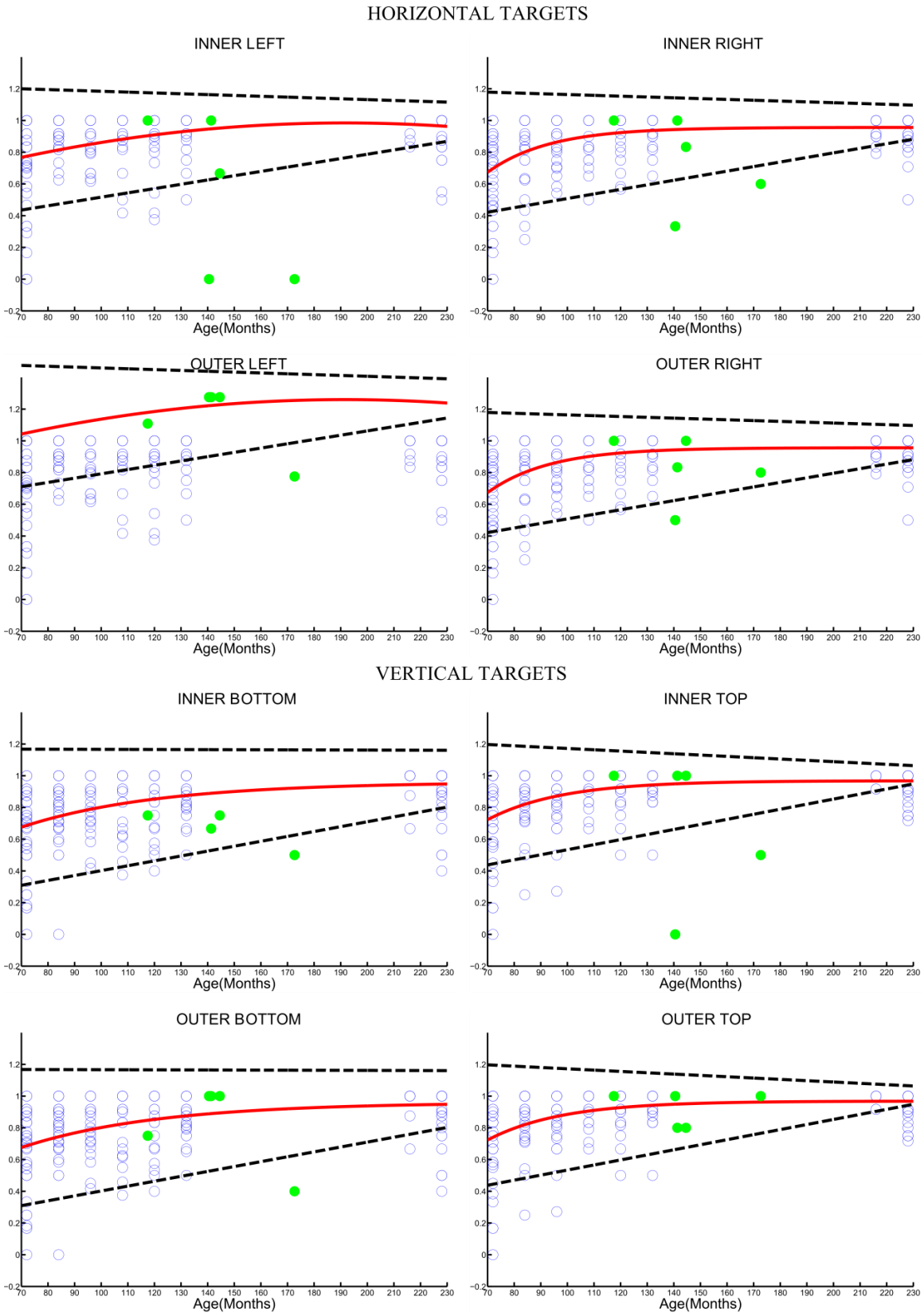


Figure 5.2.11:MPS-IVa anti-saccade error correction individual patient performance. Proportion of corrected pro-saccade errors for each target location for MPS-IVa patients (green dots). The healthy developmental trajectories of healthy controls (red line) are presented alongside 95% confidence limits (black dotted-line).

Table 5.2.11 displays the z-scores of individual MPS-IV patients. Patient 12 (14.39 years) corrected fewer saccadic errors than healthy developing controls (z-score > -2) on all inner target locations and the outer bottom target. Patient 8 (11.71 years) corrected fewer saccadic errors than healthy developing controls (z-score > -2) for all inner-target locations (patient 8 made no errors for the inner bottom target) and outer-right presented target locations. Finally, it was found that 2/5 Morquio patients produced fewer corrected errors than controls when patients' proportion of corrected errors was averaged across target locations.

Table 5.2.11: MPS-IVa z-scores for anti-saccade error corrections (*AntiCorr*)

PID	Age (Years)	Task	Target Position *Left*	*Right*	*Bottom*	*Top*	*Avg*
6	9.79	Inner	1.00 (0.69)	1.00 (0.67)	0.75 (-0.49)	1.00 (0.64)	0.92 (0.23)
		Outer	0.83 (-0.41)	1.00 (0.67)	0.75 (-0.49)	1.00 (0.64)	
8	11.71	Inner	0.00 (-5.80) **	0.33 (-3.75) **	-	0.00 (-6.50) **	0.58 (-2.88) **
		Outer	1.00 (0.49)	0.50 (-2.73) **	1.00 (0.79)	1.00 (0.53)	
9	11.78	Inner	1.00 (0.48)	1.00 (0.56)	0.66 (-1.21) *	1.00 (0.53)	0.91 (-0.13)
		Outer	1.00 (0.48)	0.83 (-0.68)	1.00 (0.79)	0.80 (-1.03) *	
10	12.05	Inner	0.66 (-1.77) *	0.83 (-0.71)	0.75 (-0.79)	1.00 (0.52)	0.89 (-0.36)
		Outer	1.00 (0.45)	1.00 (0.55)	1.00 (0.77)	0.80 (-1.08) *	
12	14.39	Inner	0.00 (-7.22) **	0.60 (-2.93) **	0.50 (-2.79) **	0.50 (-4.61) **	0.54 (-4.83) **
		Outer	0.50 (-3.53) *	0.80 (-1.27) *	0.40 (-3.45) **	1.00 (0.50)	

* *z-score > 1, ** z-score > 2*

5.2.4 Conclusions: Morquio Syndrome (MPS-IVa)

Few studies have investigated the cognitive functioning of Morquio syndrome (MPS-IVa). This is primarily due to reports of normal intellectual functioning during clinical observations (Dvorak-Ewell et al., 2010; Wraith, 2006). However, in the current study we demonstrate the existence of attention deficits on several tasks. These were most prominent for the fixation task, where fixation maintenance was disrupted by a high frequency of disruptive saccades. Deficits of simple response time and visual search time were also present, and were characterised by slower reaction time latencies on both tasks. However, these were mild in comparison to the fixation deficits. In addition, two patients produced larger search slopes than controls during feature and conjunction search. This highlights that the mechanisms of visual search (parallel and serial search) are potentially impaired in some MPS-IVa patients. Finally, MPS-IVa displayed borderline verbal comprehension difficulties on the BPVS task.

The current findings support and expand on the previous study by Davison et al. (2012), where MPS-IVa patients exhibited mild verbal comprehension deficits, and difficulties with concentration and attention (the latter reported by parents). In particular, findings from the current fixation task fit with these parental reports, since concentration problems could be reflected by difficulties maintaining attention on a visual stimulus.

Previous neuroimaging reports from MPS-IVa children have pointed to presence of frontal brain region abnormalities (Davison et al. 2012). Therefore, the prominence of attention deficits in the current cohort could be the result of from the disruption of frontal brain region functioning. In particular, the frontal eye fields (FEF) and the dorsal lateral prefrontal cortex (DLPC) have a role in suppressing reflexive saccades during fixation maintenance (Tinsley & Everling, 2002). The FEF are also associated with the production of exploratory eye movements during visual search (Booth et al., 2003), so FEF dysfunction

may relate to the observed search slope deficits. Other frontal regions that may be disrupted are the anterior cingulate and the orbitofrontal cortex, which have roles in response inhibition and decision making respectively (Bechara, Damasio, & Damasio, 2000; Booth et al., 2003; Rolls & Grabenhorst, 2008; Schoenbaum, Roesch, & Stalnaker, 2006). This is because of the general slowing of mean response time during the simple reaction time and visual search tasks that were observed in the majority of patients. However, from the present findings there is insufficient evidence to demonstrate which brain regions are disrupted in MPS-IVa. Therefore, to validate these findings it is important that future studies employ imaging techniques (such as fMRI) to examine the function of frontal regions during fixation and visual search tasks.

5.3 Hurler Syndrome (MPS-IH)

MPS-IH is caused by the deficiency of the enzyme α-L-iduronidase which in turn leads to the accumulation of dermatan and heparin sulphate. In general, two phenotypes exists: a severe early onset form (MPS-IH) and a later onset attenuated form (MPS-IA).The neurological manifestations of MPS-IH are very severe, with patients presenting with progressive learning difficulties and mental retardation. However, the severity of neurological systems in MPS-IH can be managed through the treatment of allogenic haematopoietic stem cell transplantation (HSCT) and enzyme replacement therapy (ERT). MPS-IA is associated with a variable cognitive and somatic profile, with the standard treatment being ERT.

Since treatments exist that address the cognitive features of these diseases, several studies exist (Shapiro et al., 2009, 2012; Souillet et al., 2003) that report the cognitive outcomes of patients in response to HSCT and/or ERT. Neuropsychological findings for MPS-IH and MPS-IA have revealed deficits in attention, executive functioning, and lower than average verbal IQ, with attention deficits being more pronounced in MPS-IH (Shapiro et al., 2009, 2012). It is believed that the broad range of cognitive deficits in the MPS-IH/IA are the result of both delayed myelination and progressive demyelination through the course of the disease (Müller-Forell et al., 2007). It has been argued that the differences in attention between MPS-IH and MPS-IA are the result of compromised white matter integrity caused by chemotherapy MPS-IH patients receive as part of HCT treatment (Shapiro et al., 2012). Several studies have linked white matter abnormalities to deficits of sustained attention, processing speed, and psychomotor speed (F. S. Anderson, Kunin-Batson, Perkins, & Baker, 2008; Shapiro et al., 2012). Therefore, in the current study it is predicted that patients will demonstrate deficits over a large range of tasks, with deficits being more pronounced for MPS-IH patients.

Patients

Two patients diagnosed with MPS-IH (2 males; 10.60 and 12.35 years) and 1 patient diagnosed with MPS-IA (female; age: 14.65 years) were recruited by a research nurse at Birmingham Children's Hospital (patient demographics in Table 5.3.1). Both MPS-IH patients had received a late diagnosis at 18-months of age, and received an HCT transplant at 2 years of age. All 3 patients were treated with ERT. Cognitive assessments were conducted at the Welcome Trust Clinical Research Facility at Birmingham Children's Hospital. Consent for all children was obtained from the children's parents prior to testing.

Table 5.3.1: MPS-I summary of patient demographics

PID	Gender	CA (Years)	BPVS MA (Years)	Linguistic Profile
IH 1	M	10.60	6.50	ML - English
IH 2	M	12.35	6.16	ML - English
IA 3	F	14.65	8.16	ML - English

Note: ML, monolingual, BL, bilingual

Table 5.3.2 provides a summary of findings that will be described in this section. Similar to Morquio patients, patients displayed clear deficits on the attention tasks (simple reaction time task, visual search task, fixation task, and anti-saccade task). Patients also showed difficulties on the language tasks. No deficits were evident on the pro-saccade or smooth pursuit task

Table 5.3.2: MPS-I summary of deficits across domains

Domain	Task		Notes
Attention	Simple RT Task	*	*RTmean*
	Visual Search Task	**	*VSmean*
Language	BNT	*	
	BPVS	**	
	Non-Word Task	**	*NonProd, NonComp*
Ocular Motor	Fixation Task	**	*FixDwell, FixSacc*
	Prosaccade Task	-	
	Antisaccade Task	*	*AntiCorr*
	Smooth Pursuit	-	

Note: *RTmean*, Mean Reaction Time; *VSmean*, Mean Visual Search Time; *NonProd*, Total Produced Non-Words; *NonComp*, Total Comprehended Non-Words; *FixDwell*, Fixation Duration Time; *FixSacc*, Fixation Count; *AntiCorr*; Frequency of Error Correction;
* possible deficit, ** *Consistent deficit*

5.3.1 Attention

Two of the three patients completed the attention tasks. Patient 2 (12.35 years), a MPS-IH patient, was unable to complete the attention tasks due to time constraints placed on the testing session by their clinic visit.

Simple Reaction Time Task

Comparison of the mean simple reaction time (*RTmean*) of the individual patients to the developmental trajectory of the healthy developing control population is shown in Figure 5.3.1. MPS-IH patient 1 (10.6 years) produced average response times that were clearly below the confidence limits (z-score > 2) of the healthy developmental trajectory on all 4 conditions (Table 5.3.3). In contrast, the MPS-IA patient (14.65 years) was within the 95% CI of the healthy developing trajectory for all target locations.

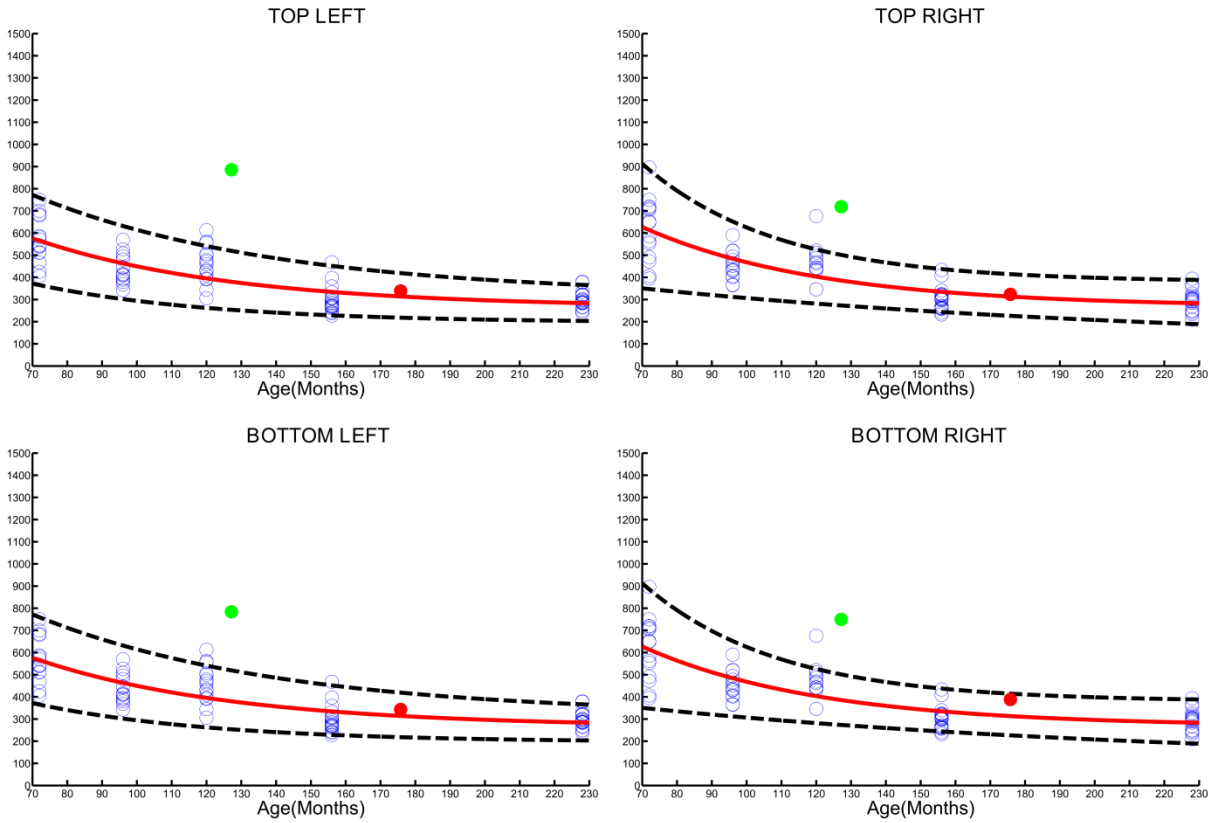


Figure 5.3.1: MPS-I simple reaction time individual patient performance. Mean simple reaction time (*RTmean*) of MPS-IH patients (green dots), MPS-IA patients (red dots) and healthy developing controls (blue dots) in comparison to a healthy developmental trajectory (red line). Reaction time is collapsed across target location for controls and the control developmental trajectory is expressed as a quadratic function with 95% CI (dashed black line).

Table 5.3.3: MPS-I z-score of simple reaction time (*RTmean*)

PID	Age (Years)	Bottom Left	Bottom Right	Top Left	Top Right	Avg
IH 1	10.6	784 (-5.67) **	749 (-6.16) **	885 (-7.10) **	719 (-5.64) **	783 (-5.77) **
IA	14.65	343 (-0.54)	388 (-1.45) *	339 (-0.46)	323 (-0.19)	348 (-0.69)

Note: Reponses recorded in milliseconds IH: MPS-IH , IA: MPS-IA , z-scores in parentheses
* *z-score > 1, ** z-score > 2*

Visual Search Task

The visual search performance of the 2 patients was examined in relation to healthy controls in terms of mean search time (*VSmean*) and search efficiency (*VSslope*) for target present trials. Patients' performance for the feature search and conjunction search is presented in Figure 5.3.2.

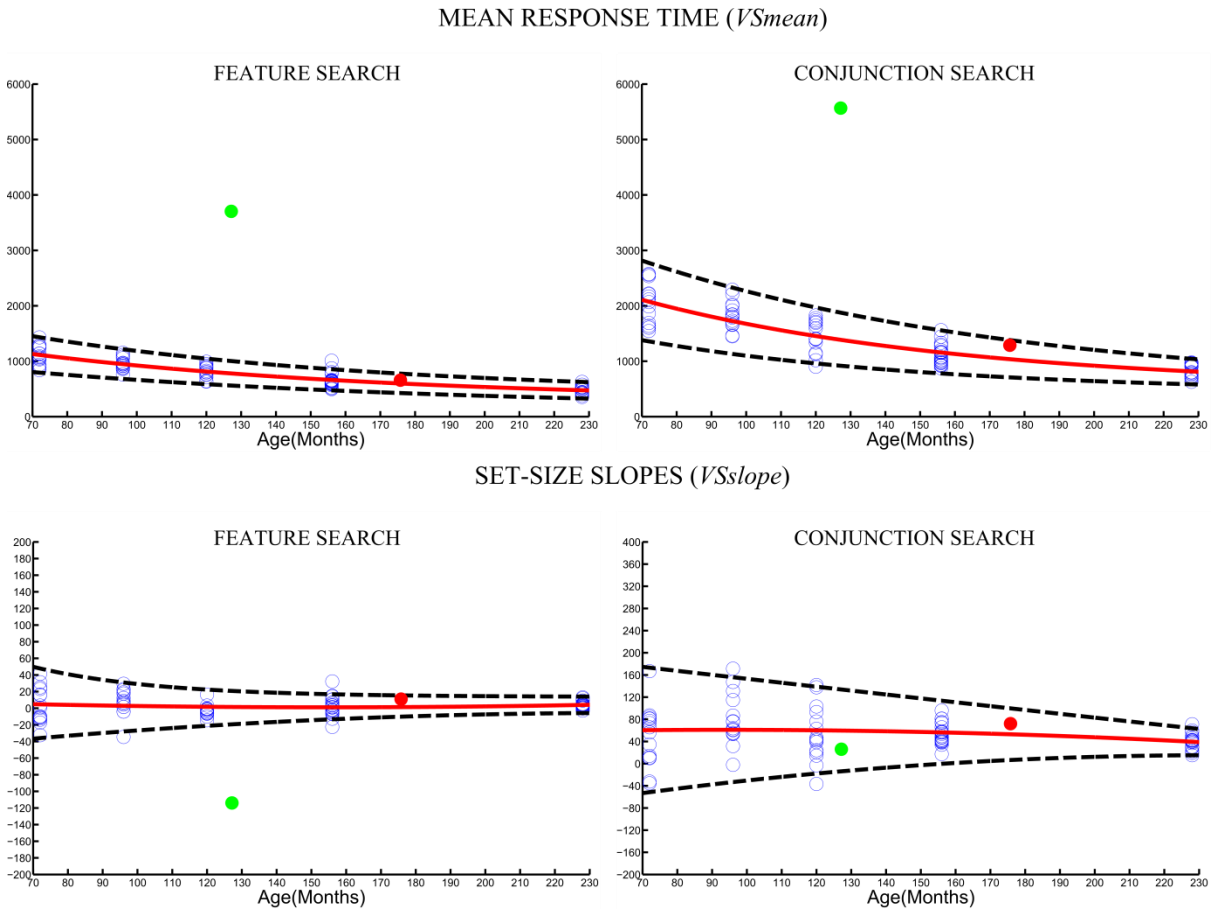


Figure 5.3.2: MPS-I visual search individual patient performance. Mean search time (*VSmean*) and search efficiency (*VSslope*) of MPS-IH patients (green dots), MPS-IA patients (red dots) and healthy developing controls (blue dots). Developmental trajectory of controls expressed as quadratic functions (red line) with 95% CI (dashed black line).

Table 5.3.4 displays the z-scores of patients on the visual search task. MPS-IH patient 1 (10.6 years) produced clear *VSmean* deficits for both feature (z-score = -25.63) and conjunction search (z-score = -16.70). MPS-IA patient 3 (14.65 years) produced search times that were within the normal range. No *VSslope* deficits were observed in either patient.

Table 5.3.4: MPS-I z-score for mean visual search time (*VSmean*) and search efficiency (*VSslope*)

PID	Age (Years)	Task	*VSmean*	*VSslope*
IH 1	10.6	FS	3704 (-25.63) **	-114 (10.83)
		CS	5566 (-16.70) **	26 (0.90)
IA	14.65	FS	658 (-0.66)	11 (-1.34) *
		CS	1289 (-1.43) *	72 (-0.81)

Note: FS: Feature Search, CS: Conjunction Search, reponses recorded in milliseconds, z-scores in parentheses
* *z-score > 1*, ** *z-score > 2*

To further clarify the reported visual search findings, response time slopes of the two patients are displayed in Figure 5.3.3.

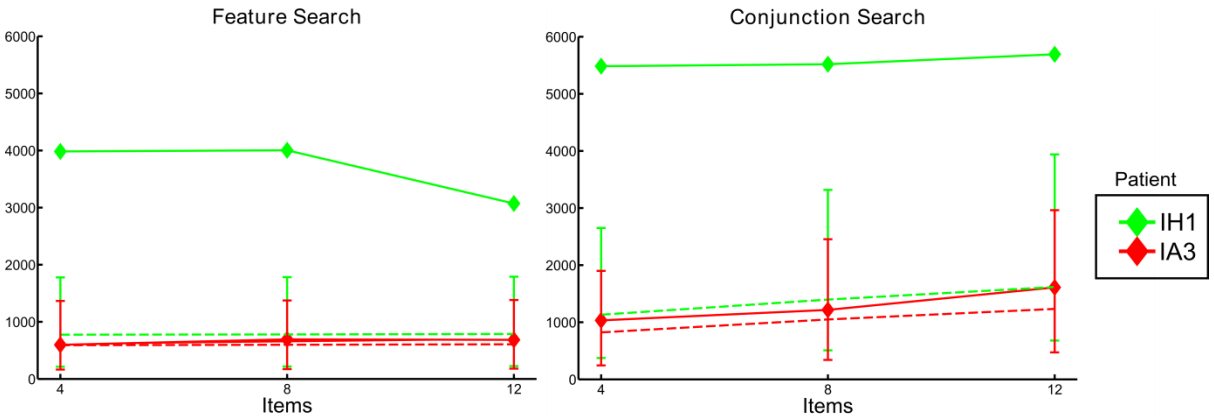


Figure 5.3.3: MPS-I visual search mean search times. *M*ean response latencies (ms) on each set size for feature search (left panel) and conjunction search tasks (right panel) for MPS-IH patient 1 (green line) and the MPS-IA patient (red line). Predicted performance of healthy controls (relative to patients' age) is shown by dash-lines. Error bars represent the 95% CI of healthy developing controls.

For MPS-IH patient 1, set size did not appear to produce search efficiency deficits for either feature or conjunction search. However, search times here are extremely slow in comparison to healthy controls which are likely to be due in part to the simple reaction time deficits reported previously. The MPS-IA patient demonstrated typical feature and conjunction search response latency slopes whereby response times increase as a function of set size for conjunction search only. Interestingly the conjunction response time slope between 8 and 12 items appeared steeper than controls. This could suggest that the MPS-IA patient may have exhibited clear search proficiency deficits if a larger array of target items (> 12) were presented.

5.3.2 Language

All 3 patients completed the 3 language tasks. No alterations were made to the study protocol in order for the patients to complete the tasks. Language deficits were observed on all 3 tasks.

Production and Comprehension

Patient verbal production scores (BNT) and verbal comprehension scores (BPVS) are reported in Figure 5.3.4 and Table 5.3.5.

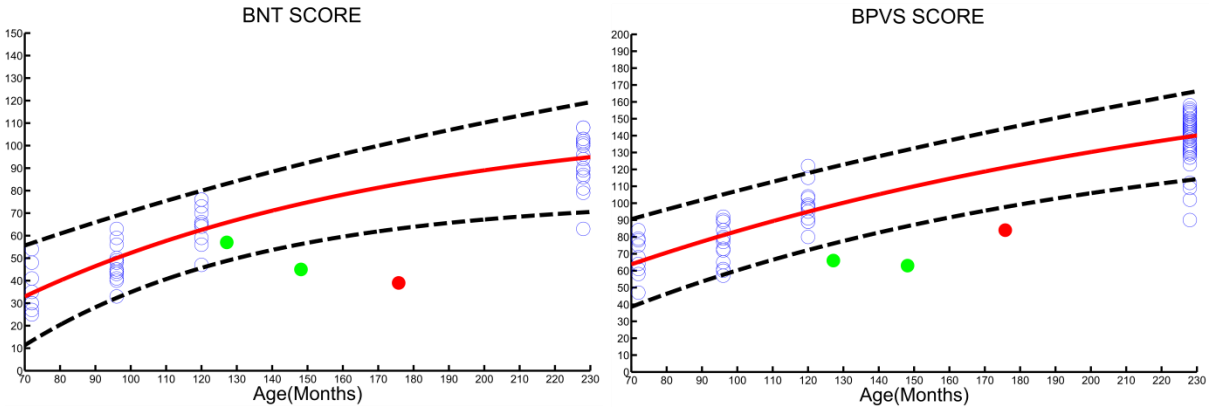


Figure 5.3.4: MPS-I verbal production and comprehension individual patient scores. MPS-IH Patient (green dots), MPS-IA (red dots) and healthy control (blue dots) raw scores on the Boston Naming task (left) and the British Picture Vocabulary Scale (right). Healthy developing trajectories (red line) are expressed as quadratic functions for both BNT and BPVS. 95% confidence limits also included (black dashed-line).

On the Boston Naming task (BNT) MPS-IH patient 2 (12.35 years) and the MPS-IA patient (14.65 years) obtained scores that were below the 95% CI (z-score > 2) of the healthy developing trajectory. MPS-IH patient 1 produced a BNT score that was within the lower range of the healthy developing trajectory (z-score > 1). Deficits were clearer for verbal comprehension for both MPS-IH patients (patient 1 and 2) and the MPS-IA patient (patient 3) whose scores were below the 95% CI of the healthy developing trajectory (z-score > 2).

Table 5.3.5: MPS-I z-scores for verbal production and comprehension

PID	Age (Years)	*BNT*	*BPVS*
IH 1	10.6	57 (-1.01) *	66 (-2.83) **
IH 2	12.35	45 (-3.19) **	63 (-3.97) **
IA	14.65	39 (-4.34) **	84 (-3.11) **

Note: z-scores in parentheses
* *z-score > 1, ** z-score > 2*

Non-word Learning Task

The non-word learning performance of patients for the 5 non-words (monsters) is displayed in Figure 5.3.5 and **Table 5.3.6**.

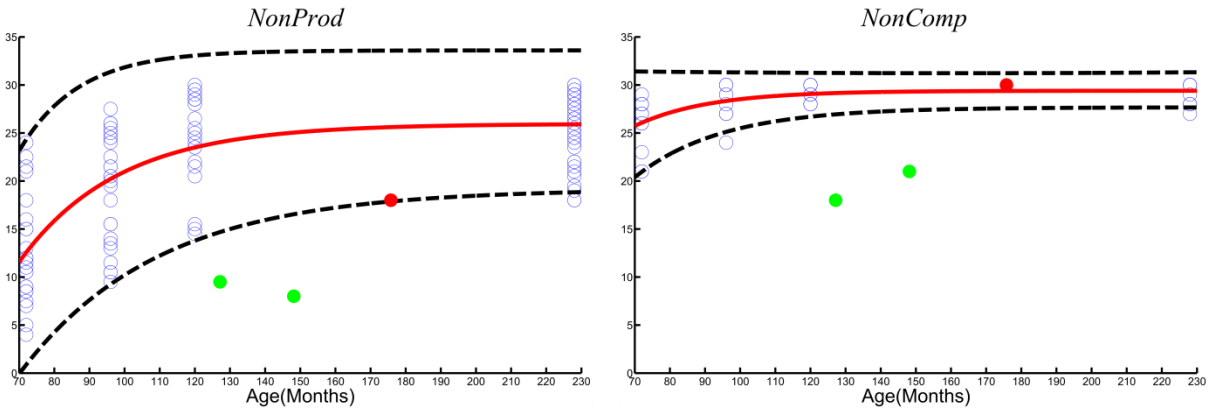


Figure 5.3.5: MPS-I non-word production and comprehension individual patient score. MPS-IH patients (green dots), MPS-IA patient (red dot), and healthy controls (blue dots) total non-word production and comprehension scores in relation to healthy developing trajectories (red lines). Production and comprehension scores are shown in the left and right panels respectively. 95% confidence limits (black dashed-lines) are included

The sum of produced monster names, over the 6 iterations of the learning phase (max score: 30), was clearly below the 95% healthy developing CI for the 2 MPS-IH patients. The MPS-IA patient (patient 3) displayed a borderline production deficit (z-score = -1.93).

Similarly, the sum of comprehended monsters was below the 95% healthy developing CI for the MPS-IH patients only.

Table 5.3.6: MPS-I z-scores for non-word production and comprehension

PID	Age (Years)	*NonProd*	*NonComp*
IH 1	10.6	8 (-3.93) **	21 (-8.34) **
IH 2	12.35	10 (-3.05) **	18 (-9.86) **
IA 3	14.65	18 (-1.93) *	30 (0.66)

Note: z-scores in parentheses
* *z-score > 1, ** z-score > 2*

The raw learning scores of the 3 patients compared to age-matched controls are presented in Figure 5.3.6. These data highlight the problems patients have for the production and comprehension of non-words. During production learning iterations, MPS-IH patients (1 and 2) were unable to correctly produce more than 2 monster names. Interestingly the MPS-IA patient (patient 3) correctly produced the names of 3 monsters during the first iteration, but was not able to name more than 2 monsters correctly in any of the remaining iterations. The comprehension slopes show that the MPS-IA patient correctly identified all 5 monsters in all 6 learning iterations. Therefore, the MPS-IA non-word production difficulties are not due to a non-word comprehension deficits. In contrast, the MPS-IH patients displayed difficulties recognising more than 4 monsters, so it is likely that MPS-IH production deficits relate in part to comprehension difficulties.

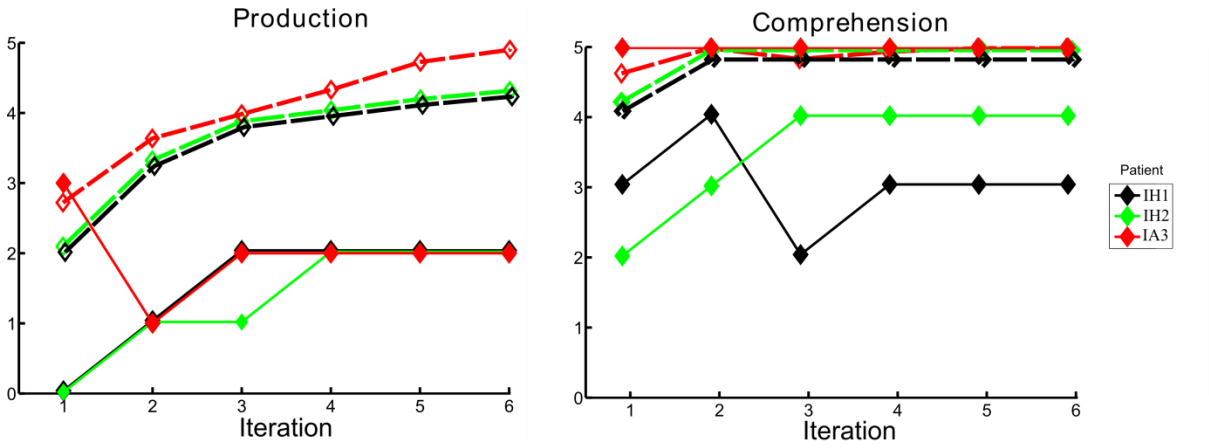


Figure 5.3.6: MPS-I non-word learning performance of individual patients. Number of monsters named and identified for by MPS-IH and MPS-IA patients for production (left panel) and comprehension (right panel) respectively. Learning slopes indicate performance during 6 successive learning iterations. Predicted performance of healthy controls (relative to patients' age) is shown by dash-lines.

5.3.3 Oculomotor

All ocular motor tasks were completed by the MPS-IA patient. MPS-IH patient 2 was unable to complete any of the ocular motor tasks due to photophobia that prevented adequate eye tracking. MPS-IH patient 1 (10.6 years) completed only the fixation task due to fatigue.

Results here are presented for the fixation task and anti-saccade task. The MPS-IA patient did not differ to healthy controls on the pro-saccade task and smooth pursuit task; these results are not reported here.

Fixation Task

The average duration (ms) that the patients fixated on the visual stimulus (*FixDwell*) for the 4 target locations is presented in Figure 5.3.7 and Table 5.3.7. Deficits (z-score > -2) were evident on horizontal target locations for both MPS-IH and MPS-IA patients. For vertical locations, patients produced shorter fixation durations than controls for bottom targets only. Borderline *FixDwell* deficits were found for the top locations for both patients.

However, even in this condition all patients were below the predicted mean of development (red line). The average fixation duration collapsed across locations was shorter than controls for patient 1 (3375 ms ; z-score = -4.20) and patient 3 (3935 ms ; z-score = -3.09).

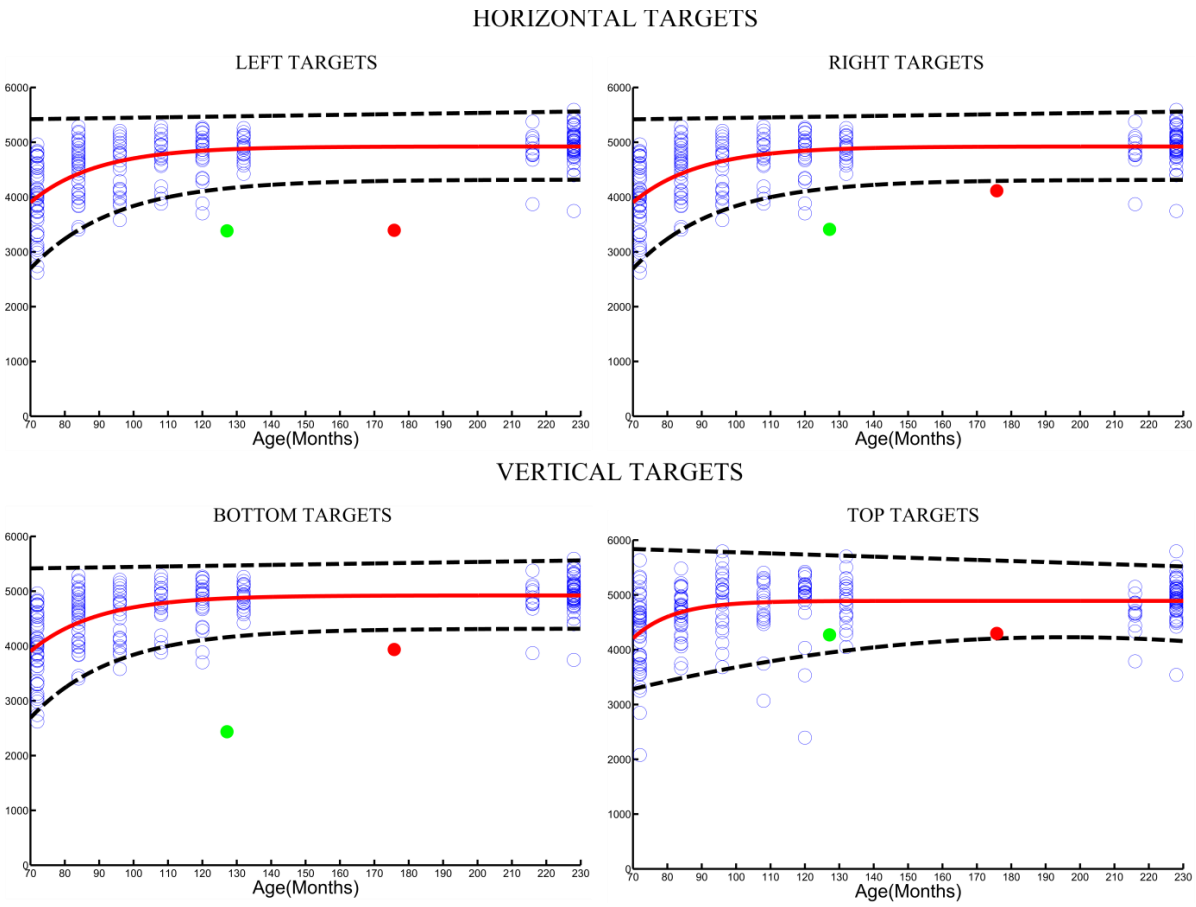


Figure 5.3.7: MPS-I fixation duration individual patient performance. Average fixation duration (*FixDwell*; ms) for MPS-IH patients (green dots), MPS-IA patients (red dots) and healthy controls (blue dots). The healthy developmental trajectory (red line) is expressed as a plateau function. 95% confidence limits (black dashed-line) are also presented.

Table 5.3.7: MPS-I z-score for fixation duration (*FixDwell*)

PID	Age (Years)	Target Position				Avg
		Left	*Right*	*Bottom*	*Top*	
1	10.6	3383 (-4.10) **	3411 (-4.02) **	2435 (-6.73) **	4270 (-1.28) *	3375 (-4.20) **
3	14.65	3393 (-4.80) **	4114 (-2.52) **	3935 (-3.09) **	4297 (-1.69) *	3935 (-3.09) **

Note: Durations recorded in milliseconds; z-scores in parentheses
* *z-score > 1*, ** *z-score > 2*

The average frequency of intrusive saccadic eye movements (*FixSacc*) is presented in Figure 5.3.8. Here patients displayed *FixSacc* deficits, or borderline *FixSacc* deficits, on all target locations.

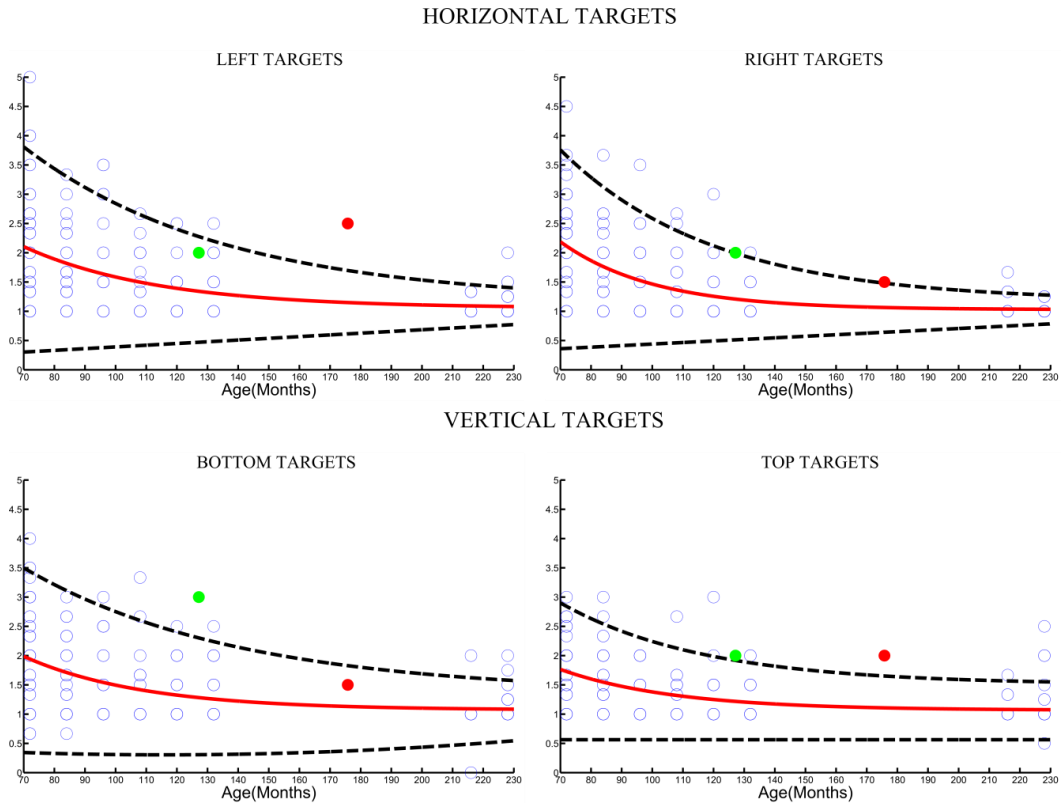


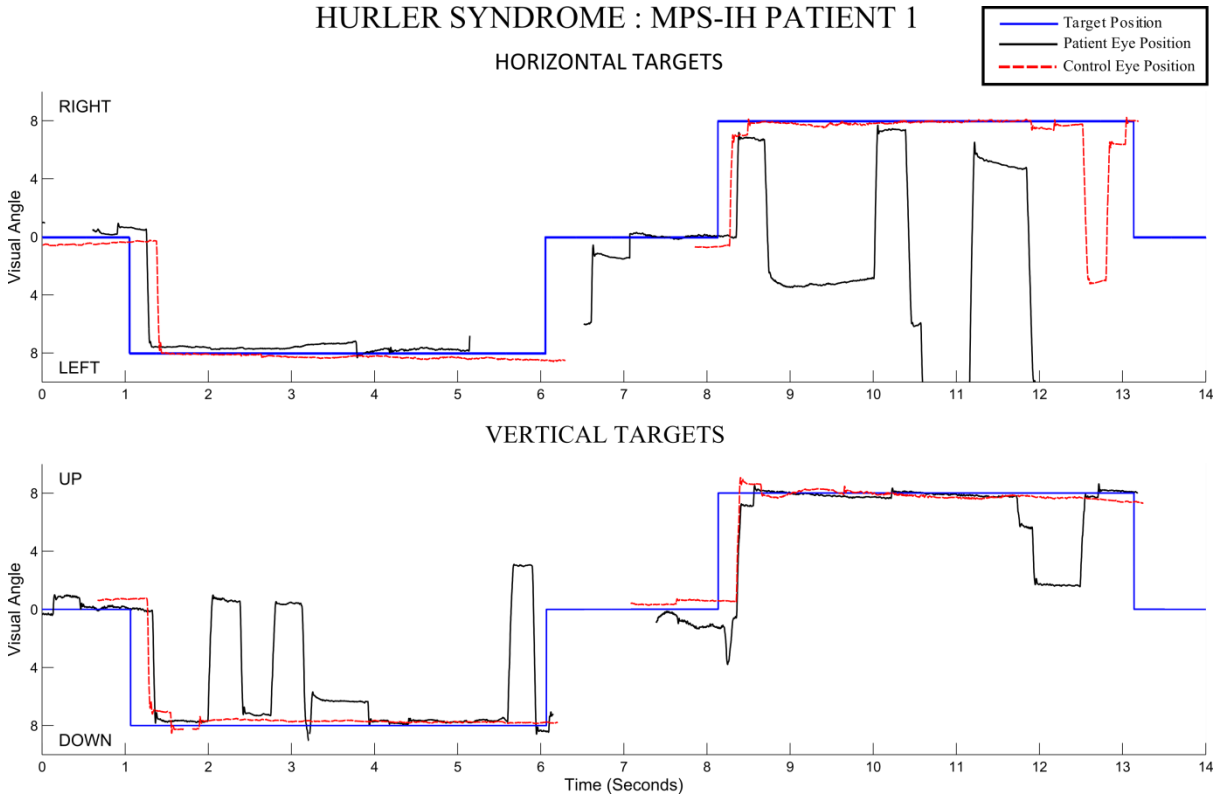
Figure 5.3.8: MPS-I intrusive saccade individual patient performance. Average frequency of intrusive saccades (*FixSacc*) produced by MPS-IH patients (green dots), MPS-IA patients (red dots) and healthy controls (blue dots). The healthy developmental trajectory (red line) is expressed as a plateau function. 95% confidence limits (black dashed-line) are also presented.

Table 5.3.8 shows that patients produced an average of 2 intrusive saccades when performance was collapsed across target locations (MPS-IH patient 1 (z-score) = - 3.39 ; MPS-IA patient (z-score) = -4.36). The temporal eye movement data of both patients (Figure 5.3.9) shows that the *FixDwell* deficits exhibited by the 2 patients were primarily due to difficulties suppressing intrusive saccades (*FixSacc*). The onset and velocity of the initial eye movements towards the target did not appear to differ between patients and controls. This means that the *FixDwell* deficits were not the result of patients' gaze reaching the target later than controls.

Table 5.3.8: MPS-I z-scores for intrusive saccades (*FixSacc*)

PID	Age (Years)	Target Position				*Avg*
		Left	*Right*	*Bottom*	*Top*	
IH 1	10.6	2 (-1.38) *	2 (-1.98) *	3 (-3.30) **	2 (-2.19) **	2 (-3.39) **
IA	14.65	3 (-4.83) **	2 (-2.06) **	2 (-1.04) *	2 (-3.22) **	2 (-4.36) **

Note: z-scores in parentheses
* *z-score > 1*, ** *z-score > 2*



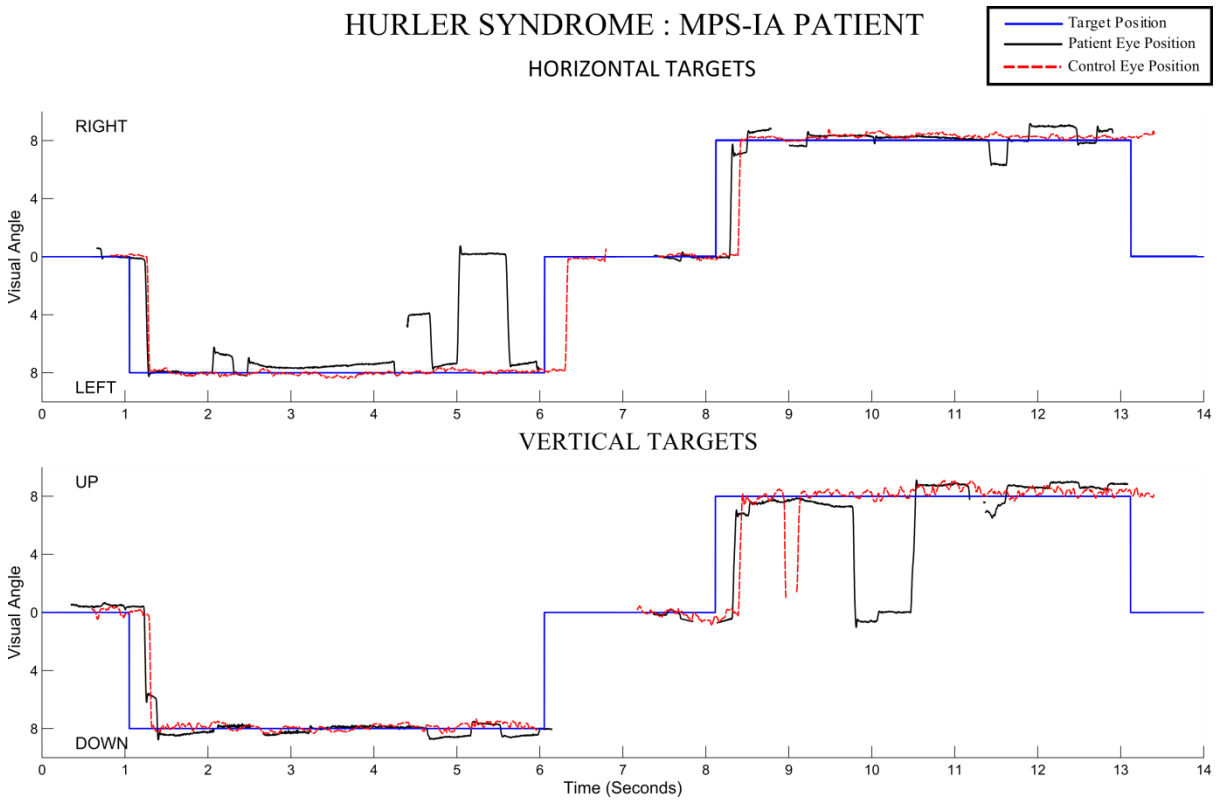


Figure 5.3.9: MPS-I fixation task raw temporal data. Fixation performance of MPS-IH patient 1 and the MPS-IA patient. The visual stimulus (blue line) is presented along with eye position (black line). For each patient the above graph shows horizontal target conditions and the below graph shows vertical conditions.

Pro-saccade Task

As expected from the eye movements shown during the fixation task (Figure 5.1.11), the reflexive properties of saccades (saccade initiation latency (*SaccOnset*) and saccade velocity (*SaccVelo*)) were within range of normal healthy controls for both patients. Consequentially these results are not presented here.

Anti-saccade Task

Only the MPS-IA patient completed the anti-saccade task and did not present deficits for the time taken to locate the anti-saccade target (*AntiOffset*). The proportion of corrected errors (*AntiCorr*) that the MPS-IA patient produced is displayed in Figure 5.3.10. For 5 of the 8 target locations the MPS-IA patient corrected fewer errors than the expected (z-score > 2). These target locations included both bottom targets (inner = .40 and outer = .20), the outer top (.75), inner left (.50) and outer right targets (.40). The average proportion of corrected errors across conditions was below the 95% CI of the healthy developing controls (*AntiCorr* = .59 ; z-score = -4.52).

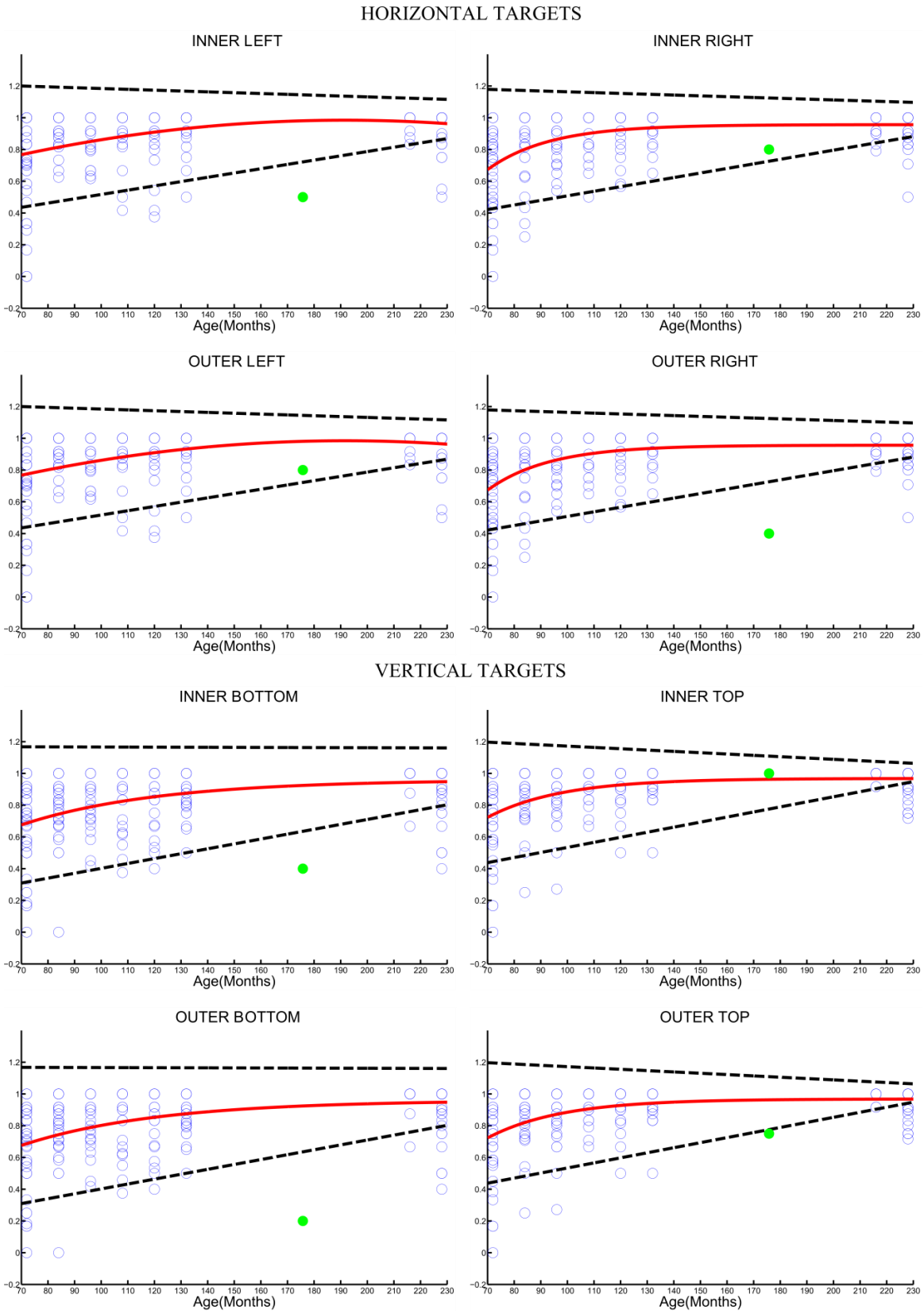


Figure 5.3.10: MPS-I anti-saccade error correction individual patient performance. Proportion of corrected pro-saccade errors exhibited by the MPS-IA patient. Target amplitudes of 4° (inner) are shown in the top four panels and target amplitudes of 8° (outer) vertical are shown in the bottom fours panels.

5.3.4 Conclusions: Hurler Syndrome (MPS-I)

The present study investigated the cognitive functioning of 3 patients (2 MPS-IH, 1 MPS-IA) diagnosed with Hurler syndrome on measures of attention, language and oculomotor function. MPS-IH, and the less severe form MPS-IA, is a lysosomal storage disorder that has been associated with a wide range of neuropsychological deficits. These include deficits in attention, executive function, and verbal comprehension (Biernacka et al., 2010; Shapiro et al., 2009). Consistent with previous studies, patients from the current study demonstrated clear deficits on measures of attention and language.

Attention deficits were characterised by delayed response latencies for simple reaction time and visual search, and difficulties suppressing intrusive saccades during fixation maintenance. Verbal production and comprehension deficits were demonstrated on the BNT and BPVS tasks respectively. In addition, the learning of non-words was abnormal in MPS-IH patients, with difficulties for recognition and production being identified. In most tasks, reported deficits were more pronounced for MPS-IH in comparison to MPS-IA.

The global nature of deficits reported in the present study supports is concurrent with findings that the white matter integrity of MPS-IH is compromised (Müller-Forell et al., 2007; Shapiro et al., 2012). Therefore, it is recommended that future analysis of the cohort implement imaging methods (such as fMRI and DTI) to elucidate the precise cortical regions that are disrupted in MPS-IH. In addition, the frequency of medical events, such as number of required transplants to obtain engraftment for HCT treatment, has been shown to correlate with white matter integrity. This is because the treatment involves the use of chemotherapy, which can lead to the degradation of white matter (Anderson et al., 2008).

5.4 Maroteaux-Lamy Syndrome (MPS-VI)

Maroteaux-Lamy Syndrome (MPS VI) is caused by a deficiency or dysfunction of the enzyme N-acetylgalactosamine- 4-sulfatase, which is required for the degradation of dermatan –sulphate (Wraith, 2006). The resulting presentation is primarily structural, including reduced growth velocity, enlarged head and chest deformities (de Almeida-Barros et al., 2012; Giugliani et al., 2007). MPS-VI is not associated with any cognitive manifestations, thus no studies exists detailing the neuropsychological profile of this population. It is hypothesised that functioning will be normal on the majority of tasks and that deficits may be present on measures that require motor responses, such as the simple reaction time and visual search tasks.

Patients

Two patients (siblings) diagnosed with Maroteaux-Lamy syndrome (MPS-VI) were recruited by a research nurse at Birmingham Children's Hospital (patient demongraphics shown in **Table 5.4.1**). Both patients completed the assessment during a routine clinic visit. All assessments were conducted at the Welcome Trust Clinical Research Facility at Birmingham Children's Hospital. Consent for all children was obtained from the children's parents prior to testing.

Table 5.4.1: MPS-VI summary of patient demongraphics

PID	Gender	CA (Years)	BPVS MA (Years)	Linguistic Profile
1	M	8.96	7.42	BL - English / Pashto
2	M	14.86	10.16	BL - English / Pashto

Note: ML, monolingual, BL, bilingual

Unlike MPS-IVa and MPS-IH, the function of MPS-VI patients was normal on most measures. The only exception was a mild verbal comprehension deficit on the BPVS.

5.4.1 Attention

Simple reaction time, as measured by the mean (*RTmean*) of simple response time, was normal for both patients. In addition the mean search time (*VSmean*) and search efficiency (*VSslope*) on the visual search task were within range of healthy development.

5.4.2 Language

Due to times constraints placed on the testing session due to clinic appointments that the patients had on the day of testing, only a measure of verbal comprehension (BPVS) was taken.

Production and Comprehension

The verbal comprehension scores of the 2 MPS-VI patients are displayed in Figure 5.4.1. Scores of both patients were below the predicted mean of healthy development (red line) and patient 2 (14.86 years) exhibited borderline difficulties. Table 5.4.2 indicated that these 2 patients were both within the lower range (z-score > 1) of healthy development, with patient 2 being close to exhibiting a comprehension deficits (z-score = -1.93).

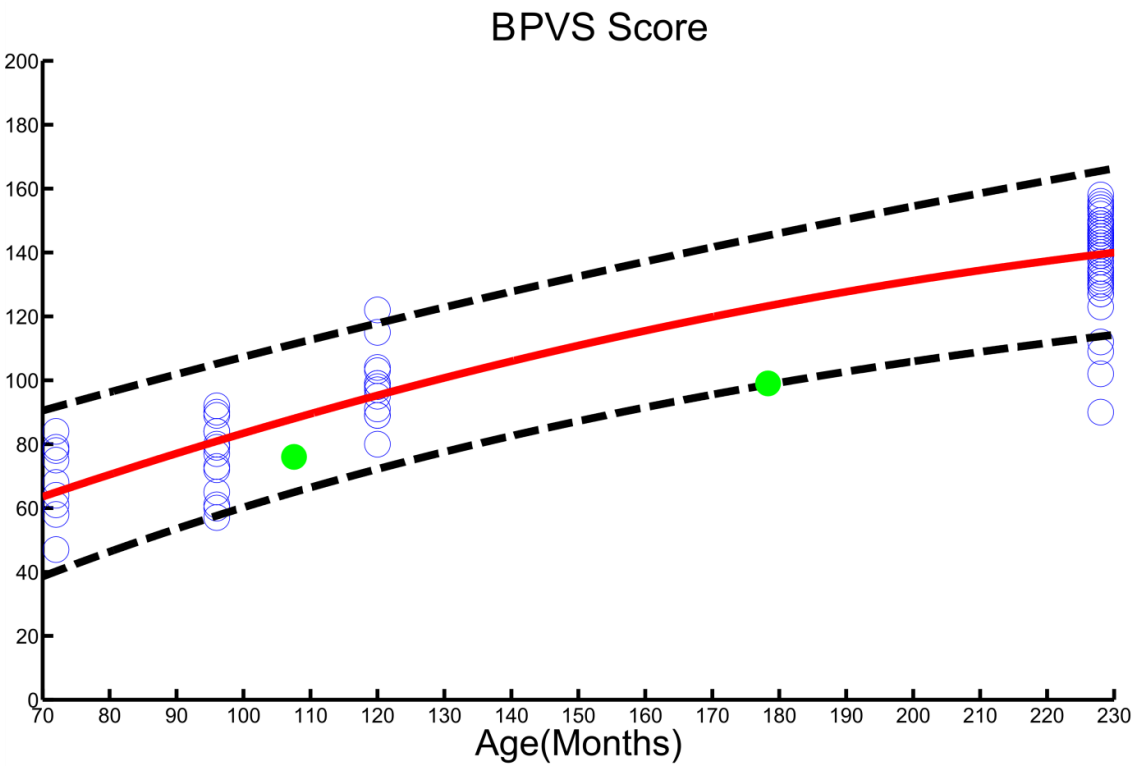


Figure 5.4.1: MPS-VI verbal production and comprehension individual patient performance. Patient (green dots) and healthy control (blue dots) raw scores on the Boston Naming task (left) and the British Picture Vocabulary Scale (right). Healthy developing trajectories (red line) are expressed as quadratic functions for both BNT and BPVS. 95% confidence limits are included (black dashed-line).

Table 5.4.2: MPS-VI z-scores for verbal comprehension.

PID	Age (Years)	BPVS
1	8.96	76 (-1.02) *
2	14.86	99 (-1.93) *

* *z-score > 1, ** z-score > 2*

5.4.3 Ocular Motor

Both MPS-VI displayed no deficits on any measure of oculomotor function. This was true for tasks that contained attentional components (fixation task and anti-saccade task) and tasks which measured the properties of ocular motor movement (pro-saccade task and smooth-pursuit task).

5.4.4 Conclusions: Maroteaux-Lamy Syndrome (MPS-VI)

The current study represented the first detailed investigation of cognitive function in children diagnosed with Maroteaux-Lamy syndrome (MPS-VI). Cognitive functioning on all measures was normal for the 2 patients. Only the eldest patient presented difficulties for verbal comprehension, and deficits here were mild. These results suggest that the cognitive function of MPS-VI children is unaffected by the disease.

5.5 Chapter Conclusions

In this chapter, the performance of 3 lysosomal storage disorders was examined: Hurler syndrome (MPS-IH), Morquio syndrome (MPS-IVa) and Maroteaux-Lamy syndrome (MPS-VI). These are disorders that have been associated with distinct neuropsychological profiles (J Ed Wraith, 2006). Cognitive functioning in MPS-IH deteriorates with disease progression (Elkin et al., 2006), MPS-IVa patients possess mild cognitive deficits (Davison et al., 2012), and MPS-VI patients are believed to possess a normal cognitive profile (Neufeld & Muenzer, 2001; J Ed Wraith, 2006). Results from the patient cohorts in the present study are consistent with these previous findings. Therefore, it was concluded that the constructed test battery which contains measures of attention, language, and oculomotor function, is sensitive to the neurodegenerative effects of metabolic disease.

In summary, both MPS-IH and MPS-IVa demonstrated prominent attention deficits. This was evident most clearly on the fixation task, whereby sustained attention was poorer for patients than controls. In addition, other attention difficulties were identified on the visual search task, whereby deficits were mild for MPS-IVa and severe for the MPS-IH patient who was assessed. This trend was similar for language tasks; mild deficits of verbal comprehension were apparent in MPS-IVa patients, and clear difficulties were exhibited for verbal production, comprehension, and non-word learning in MPS-IH. The performance of MPS-VI was normal on all tasks.

Based on the observed attention deficits in MPS-IVa and MPS-IH, it is recommended that future research investigate the functional properties of the brain regions that mediate these processes. For visual search, this would primarily involve imaging of frontal brain areas that have roles in exploratory eye movements (FEF), response inhibition (anterior cingulate), and decision making (orbitofrontal cortex). For sustained attention, the function of brain regions that are believed to be important for saccade suppression (DLPFC) should be examined.

6.0 TYROSINEMIA DISORDERS

This section of the thesis will detail findings from patients diagnosed with Tyrosinemia Type I (T1) and Tyrosinemia Type III (T3). These are disorders that are defined by the dysfunction of enzymes involved in the metabolism of tyrosine. Tyrosinemia I, the most prevalent of the tyrosinemias, is not associated with cognitive dysfunction but recent findings have suggested that long term treatment with 2-nitro-4-trifluromethylbenzoyl (NTBC) may lead mental retardation (Bendadi et al., 2014b; Masurel-Paulet et al., 2008; Thimm et al., 2012). Here we attempt to identify whether NTBC treated Tyrosinemia I patients present cognitive deficits on tasks that measure attention, language and oculomotor function. In contrast, Tyrosinemia III has been associated with intellectual impairments (Cerone et al., 1997; Ellaway et al., 2001), however these observations have been based case reports only (Ellaway et al., 2001). Hence, to our knowledge, results reported here represent the most detailed description of cognitive function in Tyrosinemia III to date.

6.1 Tyrosinemia Type I (T1)

Tyrosinemia I (T1) is caused by the deficiency of fumarylacetoacetase, the final enzyme in the tyrosine metabolic pathway, and is considered the most severe form of tyrosinemia due to liver and renal complications. If these symptoms are left untreated the accumulation of toxic metabolites, notably maleylacetoacetate and fumarylacetoace, can induce organ dysfunction and carcinogenesis, which are the main causes of early childhood death in T1. Treatment with 2-nitro-4-trifluromethylbenzoyl (NTBC) has been shown to greatly improve the survivability of patients but significantly increases tyrosine levels as a side effect. This is because NTBC biochemically switches the T1 enzymatic defect to the enzyme defect of tyrosinemia III, a disorder that is associated with elevated tyrosine levels. Due to the elevated tyrosine levels, tyrosinemia III is commonly linked with cognitive

deficits (Cerone et al., 1997; Ellaway et al., 2001). Therefore it is a concern that prolonged treatment with NTBC will lead to cognitive deficits in tyrosinemia I.

Thimm et al. (2012) and Bendadi et al. (2014a) investigated the cognitive functioning of NTBC treatment T1 patients. Using standardised measures of intelligence, both studies found that T1 patients presented with dysfunction or retardation for language development and gross motor function. Thimm et al. (2012) also investigated whether T1 patients possess neuroanatomical abnormalities, and found MRI findings to be normal in all patients. Therefore, in the current project it is expected that T1 patients will present with deficits on the language tasks. Since no neuroanatomical abnormalities have been reported in T1 patients, it is unclear how patients will perform on other tasks.

Patients

Four patients diagnosed with Tyrosinemia I (3 males; mean age: 12.53 years, range: 10.6 – 14.65 years) were recruited by a research nurse at Birmingham Children's Hospital (patient demographics shown in Table 6.1.1). All patients completed the assessment during routine clinic visits at Birmingham Children's Hospital. All assessments were conducted at the Welcome Trust Clinical Research Facility at Birmingham Children's Hospital. Consent for all children was obtained from the children's parents prior to testing.

Table 6.1.1: T1 summary of patient demographics

PID	Gender	CA (Years)	BPVS MA (Years)	Linguistic Profile
1	F	7.20	~	ML – English
2	M	8.58	5.80	ML - English
3	M	8.61	7.52	BL – English / Pashto
4	M	16.13	14.24	BL – English / Pashto

Note: ML, Monolingual, BL, Bilingual

Table 6.1.2 provides an overview of the main findings from the current cohort of T1 patients. As shown in previous studies, deficits were found on language measures (verbal comprehension (*BPVS*) and non-word learning). In addition a single patient presented a deficit for the onset latency of reflexive saccades (*SaccOnset*). Patients performed appropriately for age on tasks that contained attentional elements (simple reaction time, visual search, fixation, and anti-saccade tasks).

Table 6.1.2: T1 summary of deficits across domains.

Domain	Task		Measures
Attention	Simple RT Task	-	
	Visual Search Task	-	
Language	BNT	-	
	BPVS	*	
	Non-Word Task	*	*NonProd*
Ocular Motor	Fixation Task	-	
	Prosaccade Task	*	*SaccOnset*
	Antisaccade Task	-	
	Smooth Pursuit	-	

Note: *NonProd*: Total Produced Non-Words, *SaccOnset:* Saccade Onset Time
* Possible deficit, ** Consistent deficit

6.1.1 Attention

Three of the four patients completed all of the attention tasks during the assessment. Patient 2 (8.58 years) was unable to complete the simple reaction time task due to time constraints placed on the testing session by their clinic visit. Findings from the attention tasks revealed all patients to be within range of healthy controls on the simple reaction time and visual search tasks. Therefore these results will not be reported here.

6.1.2 Language

Due to T1 patient assessments being conducted during patient clinic visits, not enough time was available to complete all language tasks. Specifically, only patient 1 and 2 completed the British Picture Vocabulary Scale (*BPVS*), patients 2, 3 and 4 completed the non-word learning task, and no patients completed the Boston Naming task (*BNT*).

Production and Comprehension

The verbal production scores (*BPVS*) of patient 1 (8.51 years) and patient 2 (8.61 years) are displayed in Figure 6.1.1 and Table 6.1.3. Figure 6.1.1 shows that both patients exhibited scores that were below the predicted mean of healthy development (red line). Table 6.1.1 identifies a borderline deficit in patient 2 (z-score = -2.24). Since the two patients are very close in age, it is difficult to determine whether verbal comprehension deficits would exist across a wider range of ages.

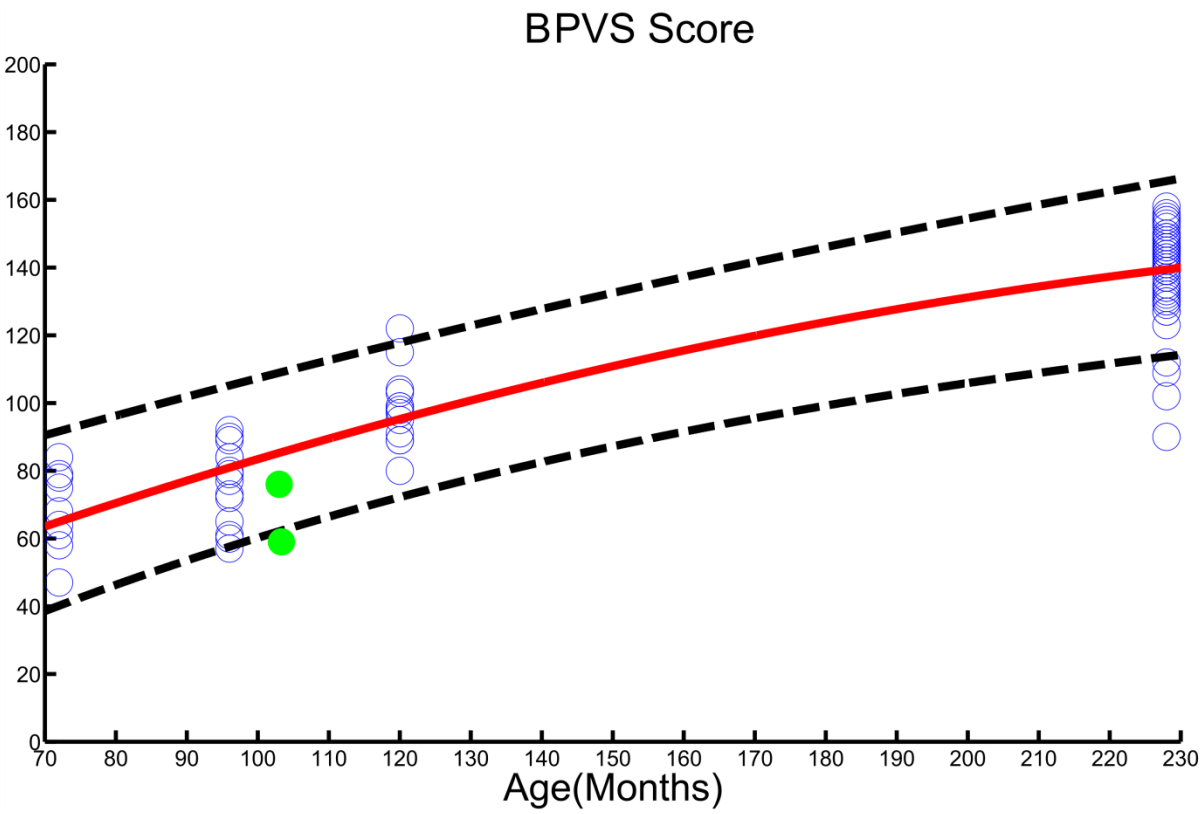


Figure 6.1.1: T1 verbal comprehension invidual patient scores. Patient (green dots) and healthy control (blue dots) raw scores on the British Picture Vocabulary Scale. Healthy developing trajectory (red line) is expressed as quadratic function. 95% confidence limits are included (black dashed-line).

Table 6.1.3: T1 z-score for verbal comprehension

PID	Age (Years)	*BPVS*
2	8.58	76.00 (-0.78)
3	8.61	59.00 (-2.24) **

Note: z-scores in parentheses
* *z-score > 1*, ** *z-score > 2*

Non-Word Learning Task

The non-word learning of 5 non-words (monsters) demonstrated by T1 patients is presented in Figure 6.1.2 and Table 6.1.4. Figure 6.1.2 shows that the performance of patient

2 and patient 3 was within the 95% CI range of healthy development (black dashed-line) for both the production (left-panel) and comprehension (right-panel). Patient 4 (16.13 years) demonstrated a borderline deficit (z-score = -2.05) for production but not comprehension. The non-word learning performance of patient 4 (Figure 6.1.3) shows that their borderline production deficit was caused by the inability to successfully produce more than 4 monster names in any of the 6 learning iterations.

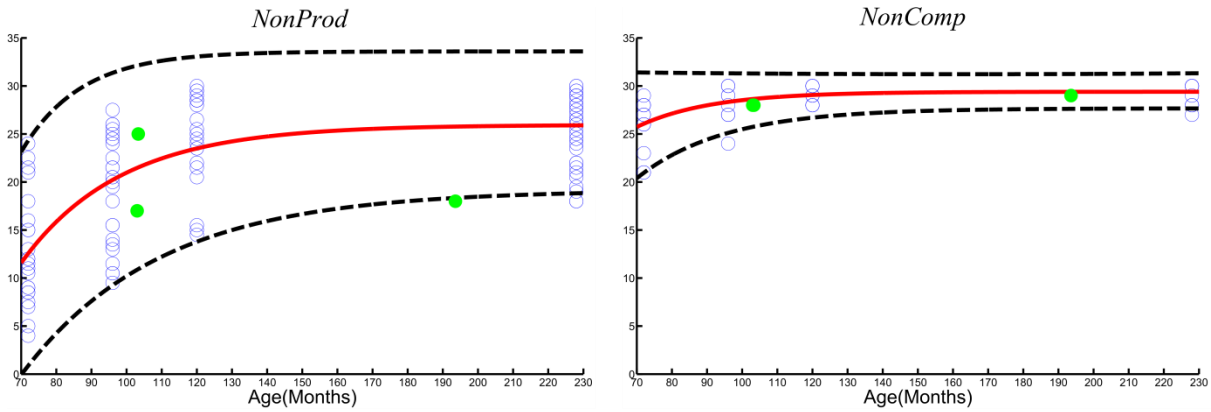


Figure 6.1.2: T1 non-word production and comprehension individual patient scores. Total non-word production and comprehension scores of T1 patients (green dots) and healthy controls (blue dots) in relation to healthy developing trajectories (red lines). Production and comprehension scores are shown in the left and right panels respectively. 95% confidence limits are included (black dashed-line).

Table 6.1.4: T1 z-scores for non-word production and comprehension

PID	Age (Years)	*NonProd*	*NonComp*
2	8.58	17 (-0.83)	28 (-0.43)
3	8.61	25 (0.64)	28 (-0.44)
4	16.13	18 (-2.05) **	29 (-0.43)

Note: z-scores in parentheses
* *z-score > 1*, ** *z-score > 2*

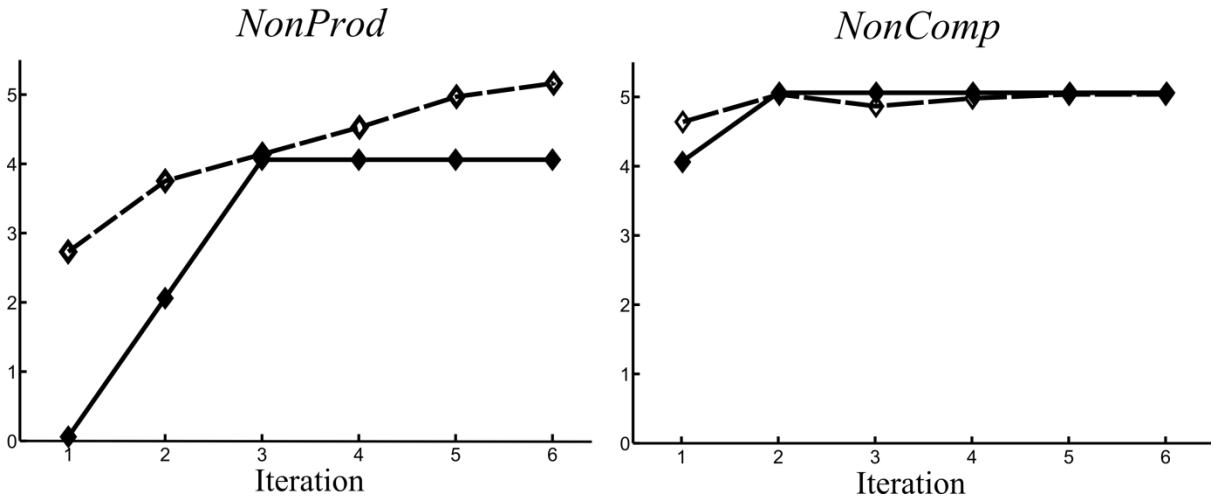


Figure 6.1.3: T1 non-word learning performance of an individual patient. Number of monsters named and identified for production (left) and comprehension (right) by patient 4 (black solid-line). Scores represent the learning over 6 successive training iterations. An age-matched control is also presented (black dashed-line)

6.1.3 Oculomotor

All T1 patients completed the oculomotor tasks. The performance of all patients was within the range of healthy development for the fixation, anti-saccade, and smooth pursuit tasks. Therefore results from these tasks will not be presented for the T1 patient group. A possible deficit was detected for the onset of reflexive saccades (*ProSacc*) during the pro-

saccade task. The velocity (*SaccVelo*) of reflexive saccades was within range of healthy development.

Pro-saccade Task

Comparison of the mean saccade onset latencies (*ProSacc*) of T1 patients to healthy developmental trajectories (red lines) is presented in Figure 6.1.4. The onset latencies of the 3 youngest patients were within the healthy developing range (black dashed-line), while the eldest patient (patient 4: 16:13 years) exhibited borderline deficits on the majority of target locations. Patient z-scores for saccade onset latency (Table 6.1.5) indicated that when the onset latencies were averaged across conditions patient 4 demonstrated a clear deficit (z-score = -2.70). An examination of patient 4's performance on individual target locations revealed that onset latencies were slower for 3/4 inner targets and 2/4 outer targets. This shows that the slower onsets that patient 4 demonstrated were not exclusive to targets positioned at specific amplitudes (inner / outer) or axes (vertical / horizontal). These findings are further illustrated by the comparison of the eye movements of patient 4 and an age-matched control which are presented in Figure 6.1.5.

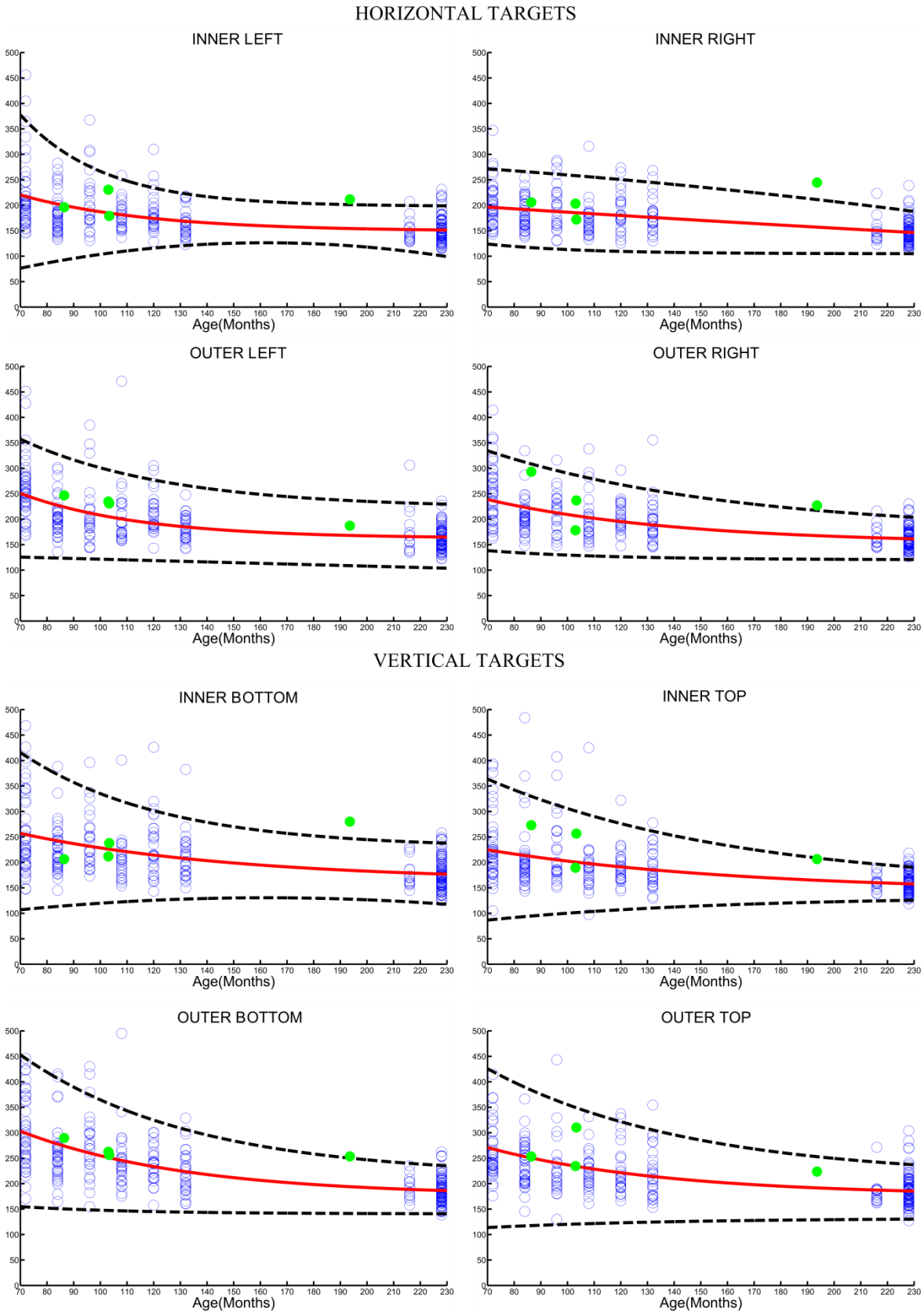


Figure 6.1.4: T1 saccadic onset individual patient performance. The average saccade onset (ms) towards the visual stimulus at each target location for T1 patients. Target amplitudes of 4° (inner) are shown in the top four panels and target amplitudes of 8° (outer) vertical are shown in the bottom fours panels.

Table 6.1.5: T1 z-scores for pro-saccade onset (*SaccOnset*)

PID	Age (Years)	Task	Target Position				*Avg*
			Left	*Right*	*Bottom*	*Top*	
1	7.20	Inner	196 (0.06)	206 (-0.39)	206 (0.53)	273 (-1.02) *	235 (-0.25)
		Outer	247 (-0.45)	293 (-1.62) *	290 (-0.24)	253 (-0.04)	
2	8.58	Inner	231 (-1.19) *	203 (-0.48)	212 (0.27)	189 (0.22)	218 (-0.22)
		Outer	235 (-0.63)	178 (0.72)	263 (-0.21)	235 (-0.00)	
3	8.61	Inner	179 (0.14)	172 (0.35)	238 (-0.23)	257 (-1.10) *	242 (-0.89)
		Outer	231 (-0.56)	237 (-0.74)	256 (-0.10)	310 (-1.30) *	
4	16.13	Inner	212 (-2.39) **	245 (-3.17) **	280 (-3.00) **	206 (-1.86) *	229 (-2.70) **
		Outer	187 (-0.55)	227 (-2.34) **	254 (-2.08) **	224 (-1.02) *	

Note: Saccade onsets recorded in milliseconds, z-scores in parentheses
* *z-score > 1*, ** *z-score > 2*

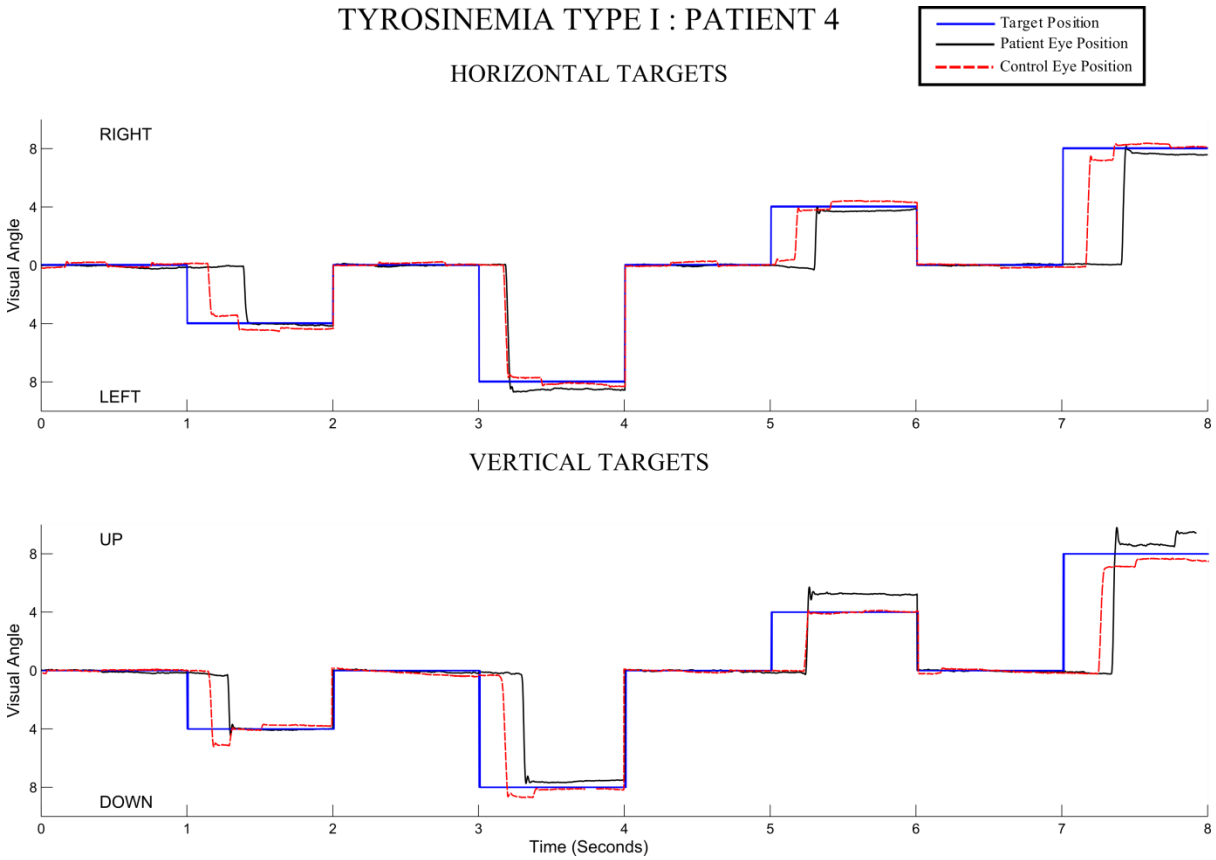


Figure 6.1.5: T1 pro-saccade task raw temporal data. Saccadic eye movements of patient 4 on horizontal and vertical target positions. The visual stimulus (blue line) is presented along with the eye position of the patient 4 (black line) and an age-matched control (red dotted-line).

6.1.4 Conclusions: Tyrosinemia I (T1)

The long-term cognitive outcomes of NTBC treated T1 patients were investigated to identify the presence of cognitive deficits using the current test battery. In the patient group (4 patients), the eldest patient (patient 4: 16.13 years) presented deficits on non-word production and reflexive saccade onset latencies. Patient 3 also presented deficits for verbal comprehension on the BPVS. Cognitive deficits were absent on tasks which measured attention and smooth pursuit eye movements.

The presence of language deficits is in line with previous findings by Bendadi et al. (2014a) and Thimm et al. (2012). However, in both these studies language deficits were reported in a larger percentage of patients (80%) compared to the current study (50%). This may be due to the smaller sample size of the current study (Thimm et al. (2012) reviewed 8 T1 patients), as a larger sample may reveal a higher percentage of patients with language deficits. In addition, Bendadi et al. (2014a) and Thimm et al. (2012) recorded the tyrosine levels, phenylalanine levels, NTBC levels, diet length, and dietary compliance of patients to evaluate how these factors affected cognitive function. In both studies, biochemical data and dietary data did not correlate with cognitive performance; patients with higher tyrosine levels did not necessarily obtain the lowest IQ scores. However, Thimm et al. (2012) stressed that future studies should monitor the biochemical data of patients to assist the interpretation of cognitive outcomes. This is because previous studies (Masurel-Paulet et al., 2008) have demonstrated that the ratio of tyrosine (raised by treatment with NTBC) to phenylalanine (reduced through the dietary intervention) may be important, as both metabolites compete for transport in the brain. A combination of high tyrosine and low phenylalanine could potentially lead to a decreased amount of phenylalanine available for the synthesis of protein and neurotransmitter. Therefore, analysing the biochemical data of the current cohort may

highlight why the older patients performed abnormally on several tasks while other patients were normal.

Based on the current findings from tyrosinemia I patients, it is unclear whether NTBC results in patients becoming susceptible to cognitive decline. While the performance of many patients was normal on tasks of attention, several patients showed deficits on language, and a single patient demonstrated difficulties initiating reflexive saccades. Future analysis should focus on incorporating biochemical data to determine whether the cognitive deficits in this cohort are linked to the ratio levels of tyrosine to phenylalanine.

6.2 Tyrosinemia Type III (T3)

Tyrosinemia Type III (T3) is a more benign form of the tyrosinemia, as it is not associated with the liver or renal complications which lead to reduced life expectancy. However, tyrosine levels are markedly elevated in T3 patients due to the deficiency of 4-hydroxyphenylpyruvate dioxygenase, the second enzyme within the tyrosine metabolic pathway. T3 is the rarest of the 3 tyrosinemias, which means only a few case studies (Cerone et al., 1997; D'Eufemia et al., 2009; Ellaway et al., 2001) exist that document the neurological and intellectual complications of the disease. However, a consistent finding is that the majority of patients present with intellectual impairments, which is believed to be due to the increase of cerebrospinal fluid tyrosine concentrations (Ellaway et al., 2001). In addition, cognitive deficits of T3 are more severe in patients who receive a later diagnosis. This is because treatment involves a tyrosine restricted diet which maintains tyrosine levels within a safe range.

The predicted cognitive performance of the current T3 cohort is difficult to determine. A series of case reports by Ellaway et al. (2001) provides the only description of

cognitive functioning for a large size sample of T3 patients (12 patients). Here, a large proportion of patients (8/12 patients) exhibited cognitive deficits which were characterised by mild to moderate learning difficulties and developmental delay. However, these reports are based solely on scores from standardised test batteries, rather than from more detailed cognitive testing. Other indicators of cognitive impairments that may be expressed by T3 patients comes indirectly from studies of NTBC treated T1 patients. This is because NTBC treatment essentially transforms T1 patients into T3 patients (from a biochemical perceptive). T1 patients who have received long term treatment with NTBC have been reported to display language development impairments (Bendadi et al., 2014a; Thimm et al., 2011). Therefore based on previous reports of T3 (Ellaway et al., 2001), it is predicted that mild to moderate deficits will be revealed across multiple domains. In addition, based on findings from NTBC treated T1 patients (Bendadi et al., 2014a; Thimm et al., 2011), moderate language deficits may also be present.

Patients

Eleven patients diagnosed with Tyrosinemia Type III (3 males; mean age: 12.53 years, range: 4.40 – 19.58 years) were recruited by a research nurse (patient demographics displayed in **Table 6.2.1**). All patients completed the assessments during appointments that were independent to their usual clinic visits at the Wellcome Trust Clinical Research Facility at Birmingham Children's Hospital. Consent for all children was obtained from the children's parents prior to testing.

Table 6.2.1: T3 summary of patient demographics

PID	Gender	CA (Years)	BPVS MA (Years)	Linguistic Profile
1	F	4.42	5.32	BL – English / Pashto
2	M	5.23	3.08	BL – Pashto / English
3	F	6.28	5.32	BL – English / Punjabi
4	M	6.62	9	ML - English
5	F	7.48	5.92	BL – English / Pashto
6	F	7.83	5.00	BL – Pashto / English
7	M	8.25	2.92	BL – English / Pashto
8	M	15.81	5.32	BL – English / Pashto
9	M	17.68	7.92	BL – Pashto / English
10	F	19.52	6.08	BL – English / Punjabi
11	F	19.81	10.32	BL – English / Punjabi

Note: ML, Monolingual, BL, Bilingual

Table 6.2.2 presents a brief summary of the findings from the T3 patients that will be discussed. Here, patients exhibited clear deficits on language tasks (*BNT* and *BPVS*). Mild attention deficits were also observed (*RTmean, VSmean, FixDwell).*

Table 6.2.2: T3 summary of deficits across domains

Domain	Task		Measures
Attention	Simple RT Task	*	*RTmean*
	Visual Search Task	*	*VSmean*
Language	BNT	**	
	BPVS	**	
	Non-Word Task	*	*NonProd, NonComp*
Ocular Motor	Fixation Task	*	*FixDwell*
	Prosaccade Task	-	
	Antisaccade Task	-	
	Smooth Pursuit	-	

Note: *RTmean*: Mean Reaction Time, *VSmean*: Mean Visual Search Time, *NonProd*: Total Produced Non-Words, *NonComp*: Total Comprehended Non-Words, *FixDwell*: Fixation Duration Time

* Possible deficit, ** Consistent deficit

6.2.1 Attention

All patients completed the attention tasks. Findings from the attention tasks will be examined on a group and individual basis. The majority of patients produced normal response times on the simple reaction time task (*RTmean*), and several patients demonstrated deficits for search time latency (*VSmean*) on the visual search task.

Simple Reaction Time Task

A comparison of the mean reaction times (*RTmean*) of individual T3 patients to the developmental trajectories of the healthy developing controls (red lines) is displayed in Figure 6.2.1. In general, the distribution of patient response times (within 95% CI range) was evenly distributed across the predicted mean healthy development (red line) on all target locations.

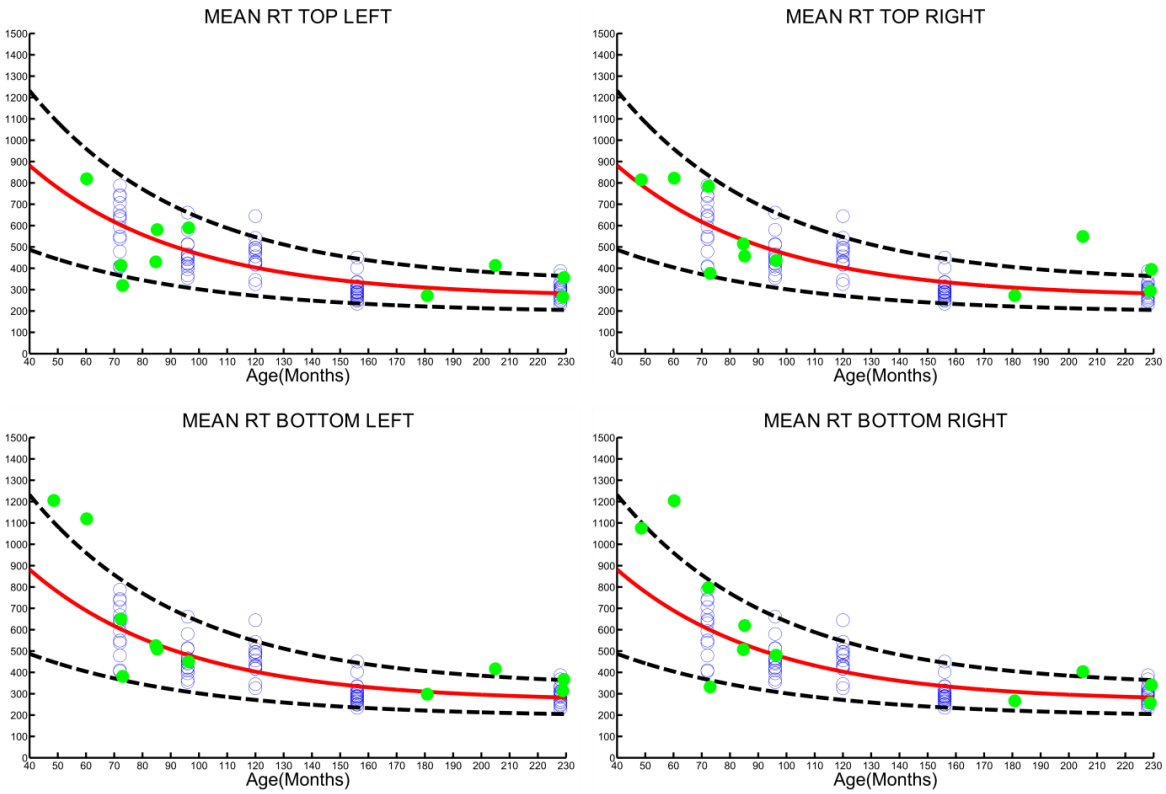


Figure 6.2.1: T3 simple reaction time individual patient performance. Mean simple reaction time (*RTmean*) of T3 patients (green dots) and healthy developing controls (blue dots). Developmental trajectory of controls expressed as a non-linear regression (red line) with 95% CI (dotted black line).

Three patients demonstrated slower response times (z-score > -2) when performance was collapsed across target locations (Table 6.2.3). These were the two youngest patients (patient 1 (4.40 years) and patient 2 (5.16 years)) and an older patient (patient 9: 17.64 years). Patient 11 (19.10 years) who exhibited a borderline response time deficit (z-score = -1.98).

Table 6.2.3: T3 z-scores for mean reaction time (*RTmean*)

PID	Age (Years)	Bottom Left	Bottom Right	Top Left	Top Right	Avg
1	4.40	1206 (-2.60) **	1075 (-1.79) *	1654 (-5.42) **	815 (-0.15)	1193 (-2.53) **
2	5.16	1119 (-3.14) **	1204 (-3.75) **	819 (-0.95)	822 (-0.98)	988 (-2.18) **
3	6.24	651 (-0.41)	797 (-1.64) *	414 (1.56)	784 (-1.53) *	661 (-0.49)
4	6.64	381 (1.81)	332 (2.22)	320 (2.33)	376 (1.86)	354 (2.04)
5	7.5	525 (0.07)	507 (0.26)	430 (1.01)	514 (0.18)	496 (0.36)
6	7.08	509 (0.21)	620 (-0.87)	581 (-0.49)	457 (0.72)	542 (-0.11)
7	8.24	450 (0.35)	480 (0.00)	590 (-1.20) *	437 (0.50)	486 (-0.06)
8	15.40	298 (0.25)	267 (0.94)	272 (0.83)	272 (0.82)	278 (0.70)
9	17.64	417 (-2.78) **	404 (-2.48) **	414 (-2.71) **	549 (-5.75) **	440 (-3.31) **
10	19.58	314 (-0.75)	257 (0.65)	266 (0.42)	294 (-0.27)	283 (-0.00)
11	19.16	367 (-2.03) **	341 (-1.41) *	356 (-1.77) *	395 (-2.71) **	365 (-1.98) *

Note: Reponses recorded in milliseconds, z-scores quotients in parentheses
* *z-score > -1*, ** *z-score > -2*

Finally, AIC comparisons revealed there was insufficient evidence of 3- and 2-way interactions, and main effects, for *Group, TargetLocation,* and *Age*. This means that t3 simple response time development was not offset from the development of heathy controls, and also the rate of development for simple response time did not differ between T3 patients and controls.

Visual Search Task

The performance of T3 patients on the visual search task is presented in Figure 6.2.2. Deficits on both feature and conjunction search tasks were identified in the younger and older patients for mean search time (*VSmean*). The 6 patients between the ages of 70-190 months exhibited normal search times.

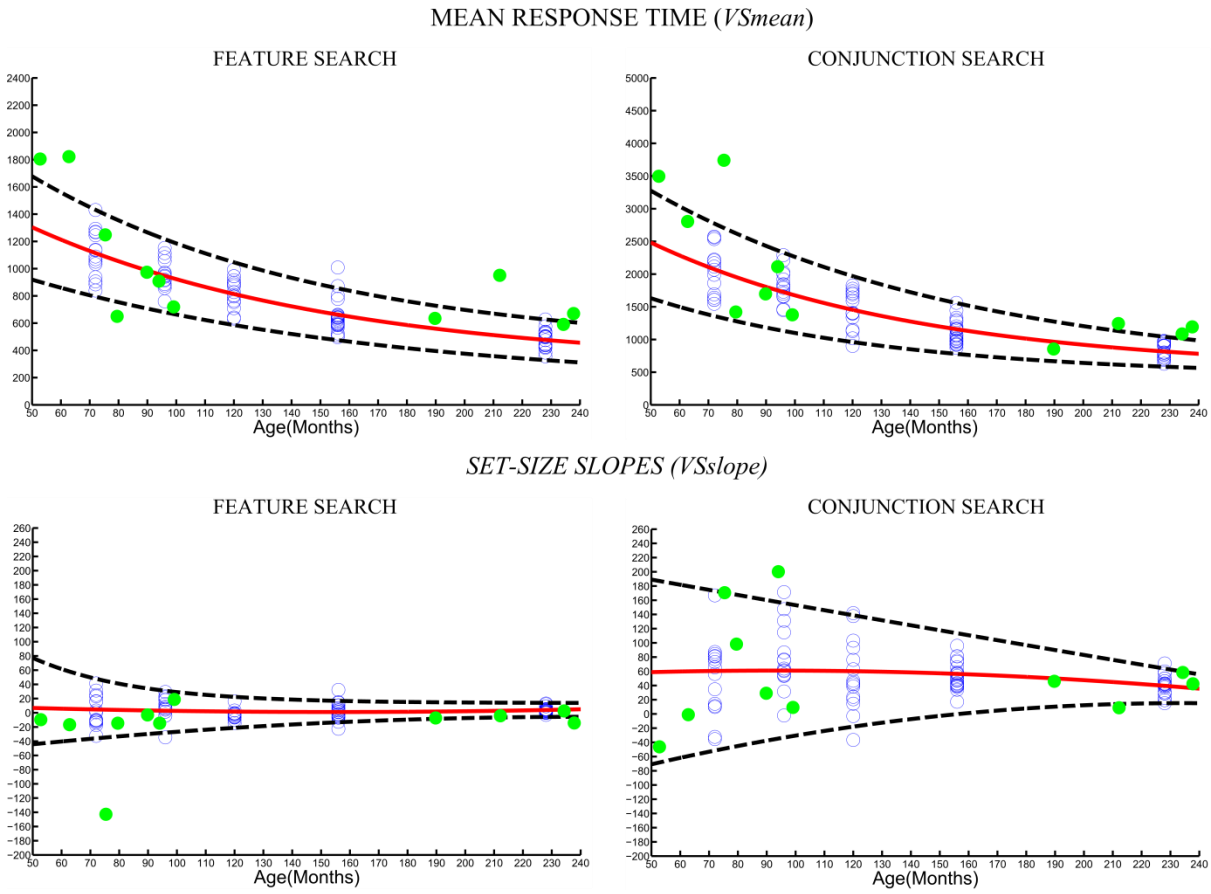


Figure 6.2.2: T3 visual search task individual patient performance. Mean search time (*VSmean*) and search efficiency (*VSslope*) of T3 patients (green dots) and healthy developing controls (blue dots). Developmental trajectories of controls are expressed as quadratic regressions (red line) with 95% CI (dashed black line).

Table 6.2.4 displays the z-scores of individual T3 patients on the visual search task. For conjunction search, only patient 6 (7.84 years) exhibited search efficiency (*VSslope*) difficulties (z-score = -2.83), however, their mean search time (*VSmean*) was still within the normal range (z-score = -1.16). As shown in Figure 6.2.2, mean search time (*VSmean*) deficits (z-score > -2) were evident among younger and older T3 patients on feature and conjunction search. Because these deficits were common for mean search time (*VSmean*) and not search proficiency (*VSslope*), it is likely that the visual search deficits are mediated by decision making, rather than serial search, deficiencies.

Table 6.2.4: T3 z-scores for visual search time (*VSmean*) and search efficiency (*VSslope*)

PID	Age (Years)	Task	*VSmean*	*VSslope*
1	4.40	FS	1805 (-2.82) **	-10 (0.64)
		CS	3496 (-2.69) **	-46 (1.62)
2	5.23	FS	1822 (-3.66) **	-17 (0.97)
		CS	2805 (-1.51) *	-1 (1.00)
3	6.28	FS	1248 (-1.01) *	-143 (7.38)
		CS	3740 (-4.92) **	171 (-1.96) *
4	6.62	FS	650 (2.65)	-15 (0.98)
		CS	1420 (1.56)	98 (-0.69)
5	7.48	FS	974 (0.09)	-3 (0.37)
		CS	1697 (0.35)	29 (0.63)
6	7.84	FS	908 (0.37)	-15 (1.10)
		CS	2112 (-1.16) *	200 (-2.83) **
7	8.26	FS	719 (1.57)	19 (-1.18) *
		CS	1378 (1.04)	9 (1.10)
8	15.81	FS	635 (-0.87)	-7 (1.74)
		CS	855 (0.73)	46 (0.20)
9	17.68	FS	951 (-5.55) **	-4 (1.46)
		CS	1243 (-2.82) **	9 (2.30)
10	19.52	FS	591 (-1.66) *	3 (0.37)
		CS	1085 (-2.62) **	58 (-1.85) *
11	19.82	FS	670 (-2.82) **	-14 (3.59)
		CS	1192 (-3.81) **	42 (-0.57)

Note: FS: Feature Search, CS: Conjunction Search, reponses recorded in milliseconds, z-scores in parentheses
* *z-score > 1,* ** *z-score > 2*

The AIC comparisons used to test for differences between the visual search developmental trajectories of patients and controls revealed insufficient evidence of 3- and 2-

way interactions for *Group, SetSize,* and *Age*. However, clear main effects for *Group* were found on feature search (test-model (ΔAIC / AIC*w*) = 0 / .999 ; null-model (ΔAIC / AIC*w*) = 35.5 / .001) and conjunction search (test-model (ΔAIC / AIC*w*) = 0 / .999 ; null-model (ΔAIC / AIC*w*) = 34.7 / .001). This means that while the rate of visual search development for T3 patients was normal for both mean search time and search efficiency, T3 development of mean search time (*VSmean*) was offset from the development of controls.

Since differences between patients and controls were reported for search time (*VSmean*) and not search efficiency (*VSslope*), only the T3 developmental trajectories for feature and conjunction search time (*VSmean*) were defined (Table 6.2.3). The fit of the developmental trajectories to linear, quadratic or plateau functions indicated that plateau functions offered the best description of development for both feature and conjunction search time (Table 6.2.5).

Table 6.2.5: T3 visual search task – AIC trajectory comparisons

Plateau Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Rate Constant	Plateau	R^2
VSmean - FS	9.5 / <.01	5.4 / .06	0 / .93	1948	.046	685	.74
VSmean - CS	3.4 / .08	0.1 / .44	0 / .47	3594	.028	1047	.64

Notes: FS: Feature Search, CS: Conjunction Search, reponses recorded in milliseconds

Developmental slopes of T3 patients and controls are presented in Figure 6.2.3. The slopes and model parameters of fitted functions (Table 6.2.5) illustrate the developmental differences that were identified between the groups. Compared to controls, at the youngest age of measurement (intercept term) T3 patients produced slower feature search (T3 =

1948ms ; Controls = 1132ms) and conjunction search responses (T3 = 3594ms ; Controls = 2074ms). However, this should be interpreted with caution since only a few patient data points occupy this time point of development. Another observation is that the development of T3 patients during later years diverges from healthy development, with patients becoming slower in comparison to healthy controls. This is because the developmental slopes of patients were defined by plateau functions, while control development was defined by quadratic functions. However, this observation should be interpreted with caution due to the small number of patient data points used to construct the patient trajectory

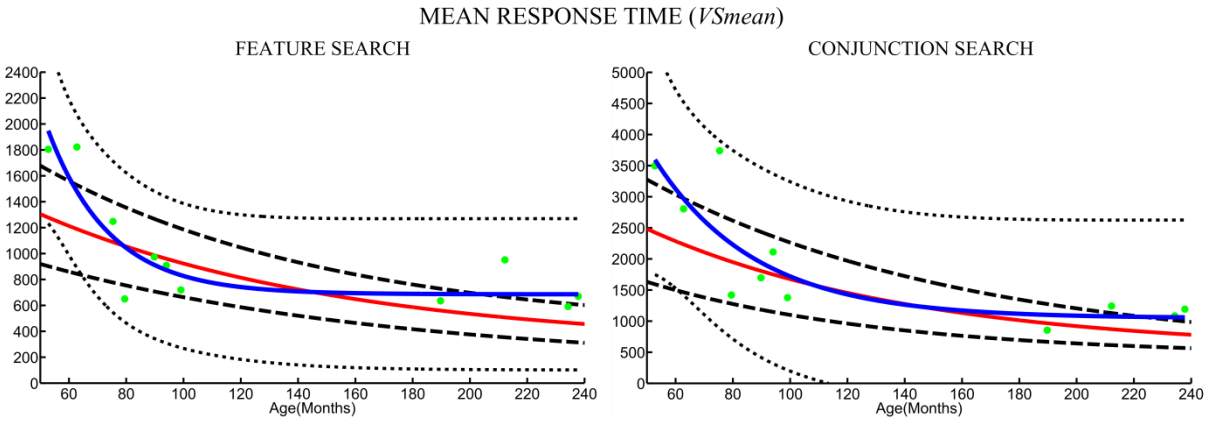


Figure 6.2.3: T3 visual search task developmental trajectories. Mean search time (*VSmean*) developmental trajectories of T3 patients (blue line) and healthy developing controls (red line). T3 patient raw scores presented as green dots. The healthy developmental trajectories are expressed as a quadratic function with 95% CI (dashed black line) for all conditions. T3 development is expressed by plateau functions with 95% prediction bands (dotted black line).

6.2.2 Language

Due to time constraints, patient 7 was unable to complete the *BNT* and 2 patients (6 & 8) were unable to complete the non-word learning task. Findings from the language tasks will be examined on a group and individual basis. Language deficits were clear for many patients on the *BNT* (vocabulary production) and the *BPVS* (vocabulary comprehension). Non-word learning deficits were less clear, as abnormalities were only apparent in two older patients.

Production and Comprehension

Patient verbal production scores (*BNT*) and verbal comprehension scores (*BPVS*) are reported in Figure 6.2.4. On both tasks, clear deficits were evident among the older patients, while borderline deficits were exhibited by younger patients.

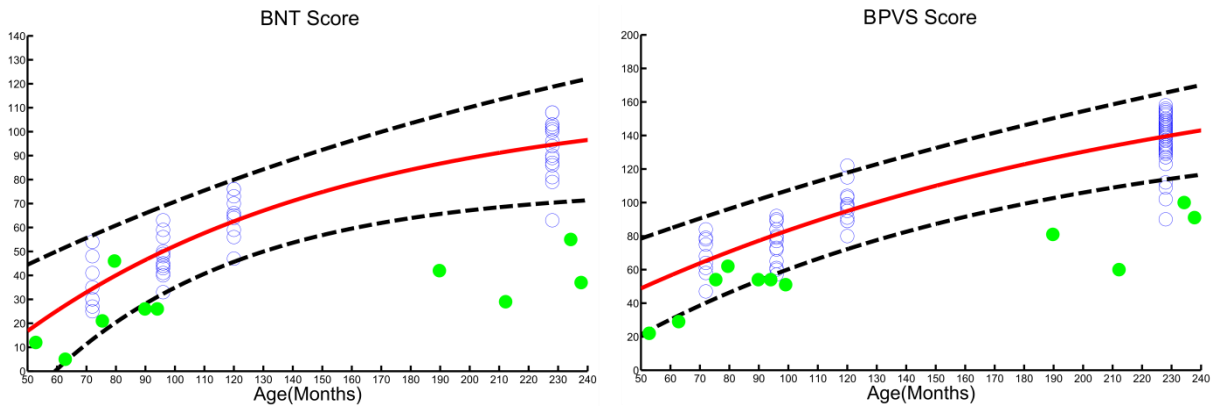


Figure 6.2.4: T3 verbal production and comprehension individual patient scores. Patient (green dots) and healthy control (blue dots) raw scores on the Boston Naming task (left) and the British Picture Vocabulary Scale (right). Healthy developing trajectories (red line) are expressed as quadratic functions for both *BNT* and *BPVS*. 95% confidence limits are included (black dashed-line).

Table 6.2.6 displays the z-scores of T3 patients on the two language tasks. Here it is evident that the majority of patients exhibited deficits (z-score > -2) on the *BNT* (6/10 patients) and the *BPVS* (8/11 patients).

Table 6.2.6: T3 z-scores for verbal production and comprehension

PID	Age (Years)	*BNT*	*BPVS*
1	4.4	12 (-0.52)	22 (-2.09) **
2	5.23	5 (-1.87) *	29 (-2.23) **
3	6.28	21 (-1.52) *	54 (-1.07) *
4	6.62	46 (0.59)	62 (-0.67)
5	7.48	26 (-2.18) **	54 (-1.91) *
6	7.84	26 (-2.51) **	54 (-2.15) **
7	8.26		51 (-2.69) **
8	15.81	42 (-4.17) **	81 (-3.73) **
9	17.68	29 (-5.36) **	60 (-5.85) **
10	19.52	55 (-3.22) **	100 (-3.11) **
11	19.82	37 (-4.64) **	91 (-3.83) **

Note: z-scores in parentheses
* *z-score > -1, ** z-score > -2*

The comparison of patient and healthy control developmental trajectories for verbal production (*BNT*) and comprehension (*BPVS*) was examined using AIC comparisons. For *BNT*, a 2-way interaction of *Group* and *Age* (test-model (ΔAIC / AIC*w*) = 0 / .93 ; null-model (ΔAIC / AIC*w*) = 5.1 / .07) and a main effect of *Group* (test-model (ΔAIC / AIC*w*) = 0 / .99 ; null-model (ΔAIC / AIC*w*) = 26.6 / <.01) was found. This suggests that the rate of development and overall performance of T3 patients differed to controls. This was also found for the *BPVS*, which was shown with in a 2-way interaction of *Group* x *Age* (test-model (ΔAIC / AIC*w*) = 0 / .93 ; null-model (ΔAIC / AIC*w*) = 5.1 / .07) and a main effect of *Group* (test-model (ΔAIC / AIC*w*) = 0 / .99 ; null-model (ΔAIC / AIC*w*) = 56.6 / <.01).

An AIC comparison of linear, quadratic, and plateau functions on the *BNT* and *BPVS* tasks for T3 patients is shown in Table 6.2.6. Comparison of AIC values (Table 6.2.7) revealed linear functions provided the best description of development for both the *BNT* and *BPVS.* Plateau functions also provided reasonably good fits to the data on the *BPVS.*

Table 6.2.7: T3 verbal production and comprehension – AIC trajectory comparisons

Linear Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates		Fit Summary
	Linear	Quadratic	Plateau	Intercept	Slope	R^2
BNT	0 / .42	1.4 / .21	0.3 / .37	18.97	.14	.38
BPVS	0 / .42	1.5 / .20	0.2 / .39	38.28	.28	.71

The developmental slopes of patients and healthy controls are presented in Figure 6.2.5. For both *BNT* and *BPVS*, the gradient of development was the primary difference between patients and controls; the developmental slopes of controls were steeper than patients. As a result, verbal production and comprehension deficits were more common among the older patients in the cohort. In addition, for BPVS development

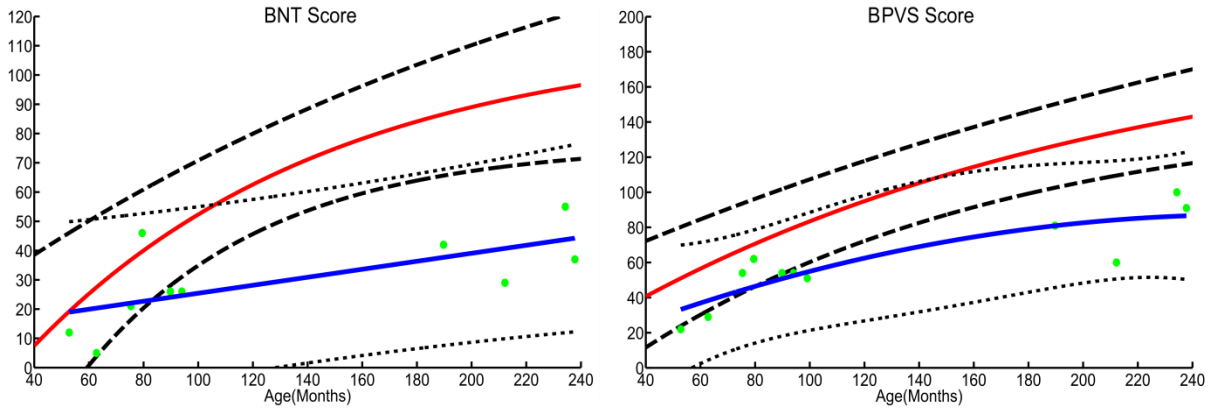


Figure 6.2.5: T3 verbal production and comprehension developmental trajectories. BNT and BPVS developmental trajectories of T3 patients (blue line) and healthy developing controls (red line). T3 patient raw scores presented as green dots. The healthy developmental trajectories are expressed as quadratic functions with 95% CI (dashed black line) and T3 developmental trajectories are expressed as linear functions with 95% prediction bands (dotted black line).

Non-Word Learning Task

The non-word learning of 5 non-words (monsters) of the T3 patients is presented in Figure 6.2.6 and Table 6.2.8.

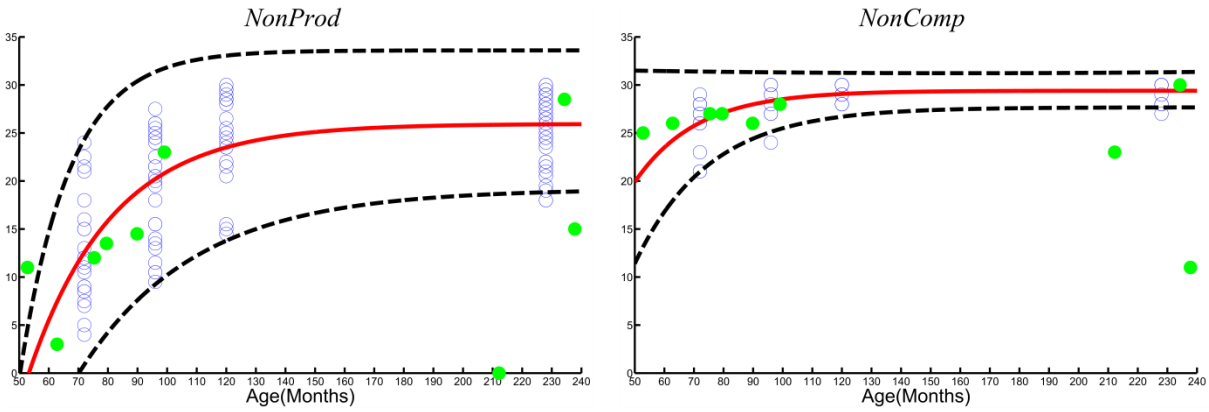


Figure 6.2.6: T3 non-word production and comprehension individual patient scores. Total non-word production and (*NonProd*) comprehension scores (NonComp) of T3 patients (green dots) and healthy controls (blue dots) in relation to healthy developing trajectories (red lines). Production and comprehension scores are shown in the left and right panels respectively. 95% confidence limits are included (black dashed-line).

Table 6.2.8: T3 z-scores for non-word production and comprehension

PID	Age (Years)	*NonProd*	*NonComp*
1	4.4	11 (4.44)	25 (0.74)
2	5.23	3 (-0.76)	26 (0.48)
3	6.28	12 (-0.35)	27 (0.18)
4	6.62	14 (-0.37)	27 (-0.03)
5	7.48	15 (-0.75)	26 (-1.08) *
7	8.26	23 (0.39)	28 (-0.31)
9	17.68	0 (-7.04) **	23 (-7.17) **
10	19.52	29 (0.66)	30 (0.61)
11	19.82	15 (-3.05) **	11 (-20.78) **

Note: z-scores in parentheses
* *z-score > 1*, ** *z-score > 2*

For the production and comprehension of non-words, the performance of the majority of patients (7 / 9 patients) was normal. Two older patients, patient 9 (17.68 years) and patient 11 (19.82 years) exhibited clear deficits for both non-word production and comprehension.

The performance of these 2 patients across the 6 learning iterations is displayed in Figure 6.2.7 against the performance of an age-matched healthy control. Here the production performance of patient 9 (red line) was at floor (no monsters were successfully named on any learning iteration), and for comprehension they were unable to identify more than 4 monsters. The comprehension performance of patient 11 (blue line) was very poor, as they could not identify more than 2 monsters. The rate of learning for production appeared similar to that of healthy controls (i.e. the difference in the number of successful named monsters between the first and last iteration was 2). However, the number of successfully named monsters in the first iteration was lower than the number of monsters named by healthy controls. Finally, an AIC comparison of developmental trajectories indicated that the development of T3 patients did not differ to the development of controls.

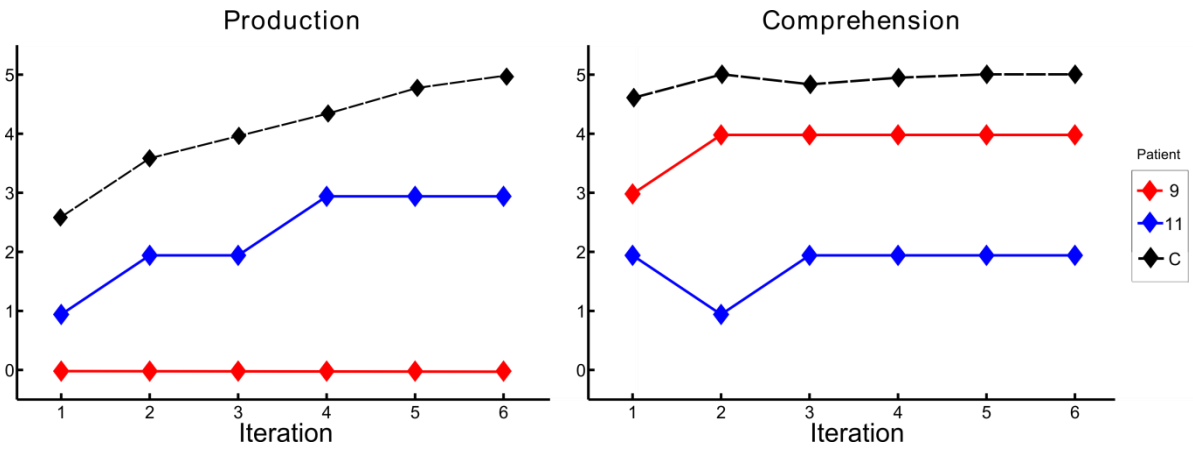


Figure 6.2.7: T3 non-word mean individual patient performance. Number of monsters named (left) and identified (right) during the non-word learning task by patient 9 (red line) and patient 11 (blue line). Learning slopes represent learning performance throughout the 6 training iterations. Predicted performance of a healthy control (relative to the age of both patients) is representesd by a black dashed-line (C).

6.2.3 Oculomotor

Ten of the eleven T3 patients completed the oculomotor tasks. One patient (patient 2) could not complete the tasks due to postural difficulties which prevented eye tracking. Patients demonstrated difficulties on the fixation task (*FixDwell* and *FixSacc*) only.

Fixation Task

The average duration that T3 patients fixated on the visual stimulus (*FixDwell*) at each target position is presented in Figure 6.2.8. As a group, the distribution of patient data points was shifted below the predicted mean of healthy development (red line).

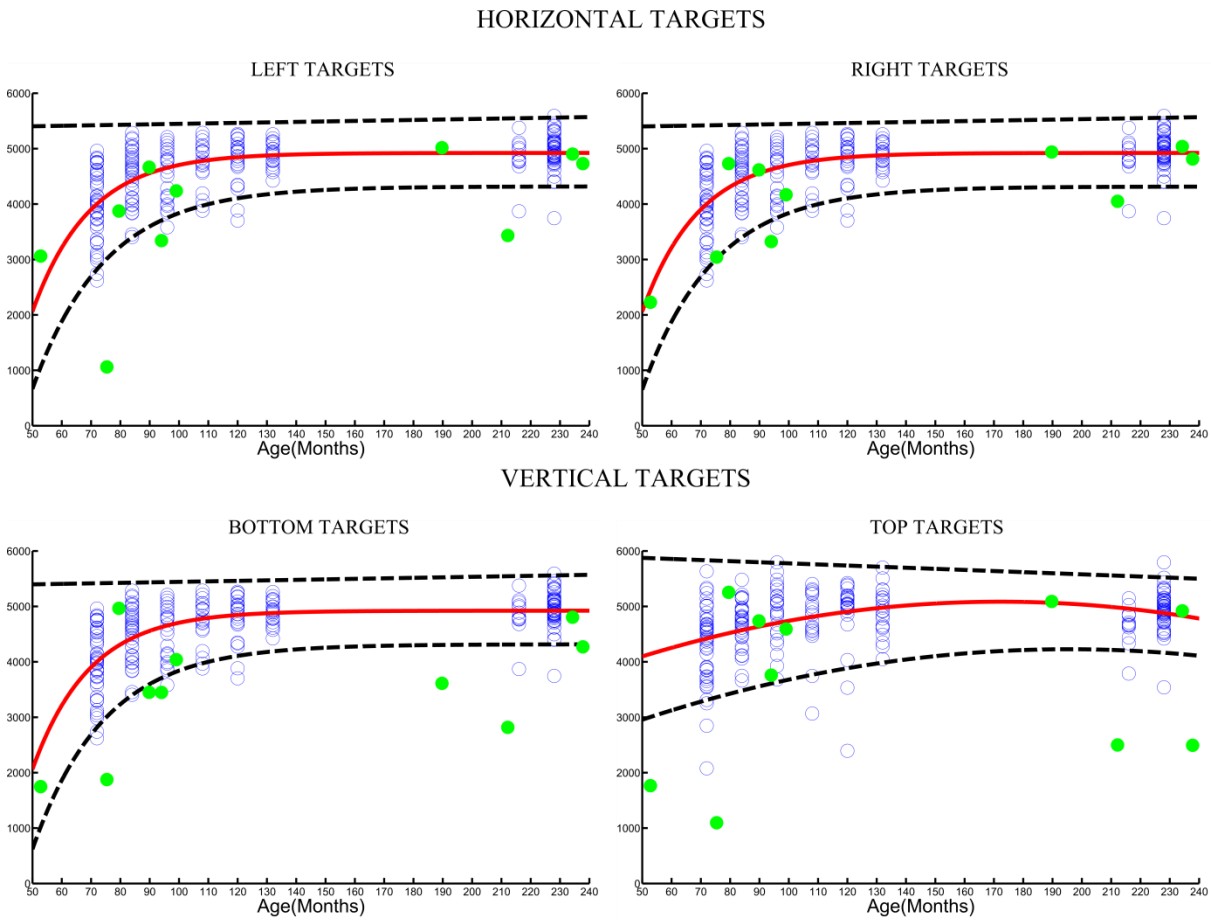


Figure 6.2.8: T3 fixation duration individual patient performance. Average fixation duration (*FixDwell*; ms) for T3 patients (green dots) and healthy controls (blue dots). The healthy developmental trajectory (red line) is expressed as a plateau function for left, right and bottom targets. A quadratic function is used here for top target development since normative predictions based on a plateau function were poor for the youngest patient. 95% confidence limits (black dotted-line) are presented.

Table 6.2.9 displays the *FixDwell* z-scores of individual T3 patients for specific target locations and for *FixDwell* averaged across targets. For the latter, 4 of the 10 patients (patient 3, 6, 9, 11) exhibited fixation duration deficits. In addition, from the inspection of individual target locations it is clear that deficits were more prevalent on bottom targets (6 / 10 patients).

Table 6.2.9: T3 z-scores for fixation duration (*FixDwell*)

PID	Age (Years)	Target Position *left*	*Right*	*Bottom*	*Top*	*Avg*
1	4.40	3062 (-0.46)	2228 (-1.08) *	1748 (-1.42) *	1766 (-4.09) **	2201 (-1.25) *
3	6.28	1061 (-5.33) **	3043 (-1.91) *	1875 (-3.91) **	1096 (-6.00) **	1762 (-4.44) **
4	6.62	3874 (-0.76)	4730 (0.75)	4966 (1.16)	5254 (1.06)	4706 (0.64)
5	7.48	4665 (0.24)	4617 (0.14)	3450 (-2.25) **	4738 (-0.04)	4367 (-0.47)
6	7.84	3340 (-2.74) **	3323 (-2.77) **	3448 (-2.51) **	3760 (-1.71) *	3468 (-2.64) **
7	8.26	4238 (-1.02) *	4168 (-1.18) *	4040 (-1.47) *	4593 (-0.41)	4260 (-1.06) *
8	15.81	5017 (0.31)	4939 (0.06)	3612 (-4.16) **	5089 (0.55)	4735 (-0.60)
9	17.68	3433 (-4.79) **	4050 (-2.80) **	2818 (-6.76) **	2500 (-6.89) **	3200 (-5.47) **
10	19.52	4902 (-0.07)	5039 (0.36)	4805 (-0.38)	4920 (0.09)	4916 (-0.04)
11	19.82	4730 (-0.62)	4813 (-0.35)	4271 (-2.10) **	2494 (-6.10) **	4077 (-2.71) **

Note: Durations recorded in milliseconds, z-Scores in parentheses
* *z-score > 1*, ** *z-score > 2*

The comparison of T3 patient and healthy developmental trajectories during the fixation task was examined through the comparison of AIC model values. A test for a 3-way interaction of *Group*, *Targetlocation* and *Age* (test-model (ΔAIC / AIC*w*) = 0 / .74 ; null-model (ΔAIC / AIC*w*) = 2.1 / .26) revealed that the influence of target location on the rate of fixation duration development differed between patients and controls. For patients alone, a series of 2-way interactions between *Targetlocation* and *Age* was conducted to identify how target location influenced patient development rate. This included a 1-term model with a single trajectory representing all target locations ('Combined' model), a 2-term model with separate trajectories for horizontal and vertical targets ('Hori/Vert' model), and four 2-term models which each specified a separate trajectory for the four targets

('Left','Right','Top','Bottom' models), and a 3-term model with a single trajectory representing horizontal targets, and separate trajectories representing top and bottom targets ('Hori/Top/Bottom' model). Results of this analysis are presented in Table 6.2.10. Here the model that offered the best description of T3 developmental change across the target locations was the 'Hori/Top/Bottom' model (ΔAIC = 0 ; AIC*w* = .44). This means that the sustained fixation development of T3 patients proceeded at different rates for top, bottom and horizontal targets. These findings also clarify why a 3-way interaction existed; the rate of development in healthy controls differed only on top target (described in Chapter 4), while patients exhibited different developmental rates for bottom targets, in addition to top targets.

Table 6.2.10: T3 fixation duration – AIC condition comparisons

Fix*Dwell* Model	ΔAIC	AIC*w*	Evidence ratio
Hori/Top/Bottom	0	.44	1
Hori/Vert	1	.27	1.6
Top	2	.17	2.6
Combined	4.8	.04	10
Right	5.1	.03	13
Bottom	5.6	.03	16
Left	7.5	.01	40

Since the T3 patient development across target locations was best described by the 'Hori/Top/Bottom' model, the fit of developmental trajectories to linear, quadratic or plateau functions was analysed separately for the top, bottom, and horizontal target locations. Results revealed that a linear, quadratic and plateau function best described T3 fixation duration development for horizontal, top and bottom targets respectively (Table 6.2.11). The developmental slopes of T3 patients (blue lines) on the 3 target conditions are presented in Figure 6.2.9 alongside healthy developmental trajectories (red lines). Here rates of development appeared to be similar between patients and controls for horizontal and bottom

target locations. In contrast, development rates appeared to differ between T3 patients and controls for the top target, since the slopes diverge during later years. This is because of the extreme low scores produced by older T3 patients, which explain why a quadratic function offered a preferable fit to the patient data. On all 3 target locations, T3 developmental slopes were offset below the slopes of healthy controls.

Table 6.2.11: T3 fixation duration – AIC trajectory comparisons

Linear Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates		Fit Summary
	Linear	Quadratic	Plateau	Intercept	Slope	R^2
Horizontal	0 / .40	.8 / .26	.3 / .34	3242	103	.31

Quadratic Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Linear Term	Quadratic Term	R^2
Top	.9 / .27	0 / .44	.9 / .28	1925	787	-46	.09

Plateau Models

	AIC Results (ΔAIC / AIC*w*)			Model Parameter Estimates			Fit Summary
	Linear	Quadratic	Plateau	Intercept	Rate Constant	Plateau	R^2
Bottom	.4 / .38	2.3 / .15	0 / .47	1690	.647	3917	.20

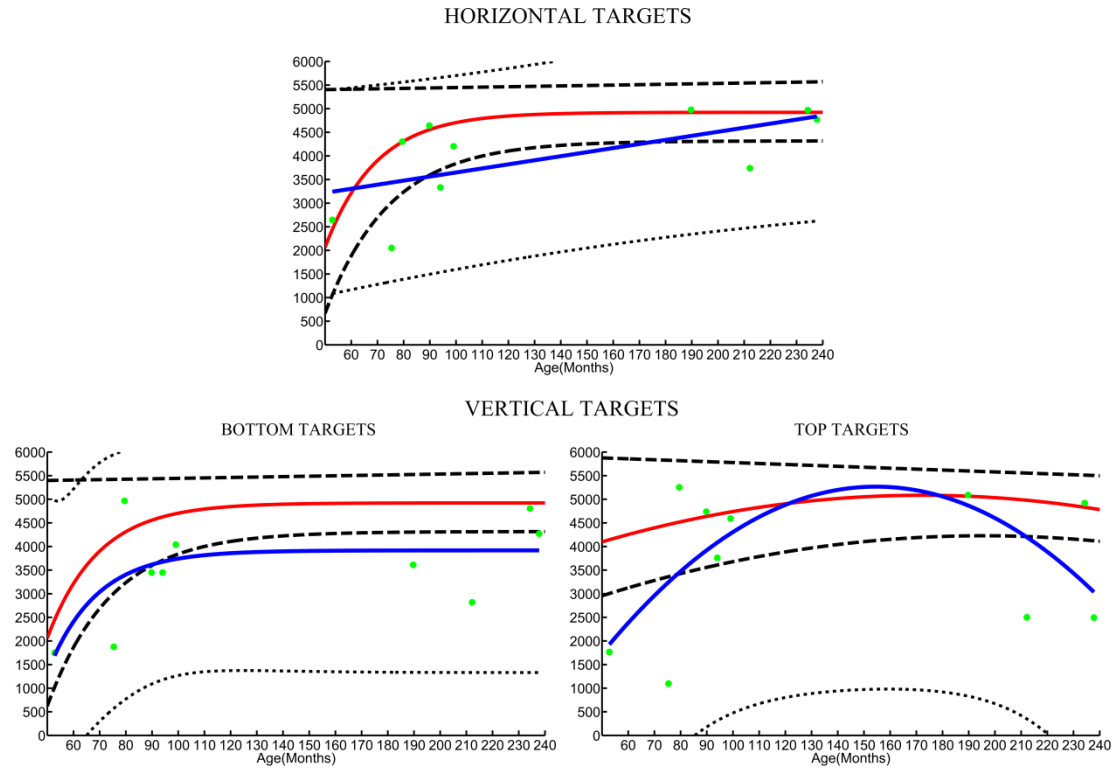


Figure 6.2.9: T3 fixation duration developmental trajectories. Fixation Duration (*FixDwell)* developmental trajectories of T3 patients (blue lines) and healthy controls (red lines). Patients raw scores presented as green dots.

In the final stage of the analysis, the developmental trajectories of patients and controls were combared independently for top, bottom, and horizontal targets. Table 6.2.12 presents the results from AIC comparisons of models that compared the main effect of *Group* and 2-way interaction for *Group* and *Age*. Main effects were very clear between groups for each comparison. The 2-way interactions for *Group* and *Age* were not evident for bottom or horizontal targets, and an interaction model was marginally better for the top target. However, when 3 patients (patient 2, 9 and 11) with extreme low dwell times were removed, a null-model was much better (test-model (ΔAIC / AIC*w*) = 2 / .27 ; null-model (ΔAIC / AIC*w*) = 0 /.73). Therefore, the interaction was largely due to the fixation performance of these 3 patients. Together these results suggest that patients' rate of development matched that of controls for all targets. However, the developmental trajectories of patients were clearly offset from those expressed by controls.

Table 6.2.12: T3 fixation duration – AIC condition comparison with healthy controls

Fix*Dwell*	*Group* Main effect AIC results (ΔAIC / AIC*w*)		*Group* x *Age* Interaction AIC results (ΔAIC / AIC*w*)	
	Test model	Null model	Test model	Null model
Top	0 / .99	16 / <.01	0 / .63	1.1 / .37
Bottom	0 / .99	15 / <.01	2 / .27	0 / .73
Horizontal	0 / .96	6 / .04	1.4 / .33	0 / .67

The average frequency of saccadic eye movements away from the visual stimulus that T3 patients produced (*FixSacc*) is presented in Figure 6.2.10 and Table 6.2.13. Here *FixSacc* frequencies were normal for the majority of younger patients (8/10 patients). Two older patients (patient 9 and 11) exhibited *FixSacc* deficits for multiple target locations and when performance was collapsed across locations (patient 9 (z-score) = -8.89; patient 11 (z-score) = -2.70). Interestingly these patients also exhibited *FixDwell* deficits, so it is likely that the observed *FixDwell* deficits resulted from *FixSacc* deficits. This can be seen in the temporal eye movement data of patient 9 (Figure 6.2.11); fixation on the target was clearly disrupted by disruptive saccades made towards the screen centre.

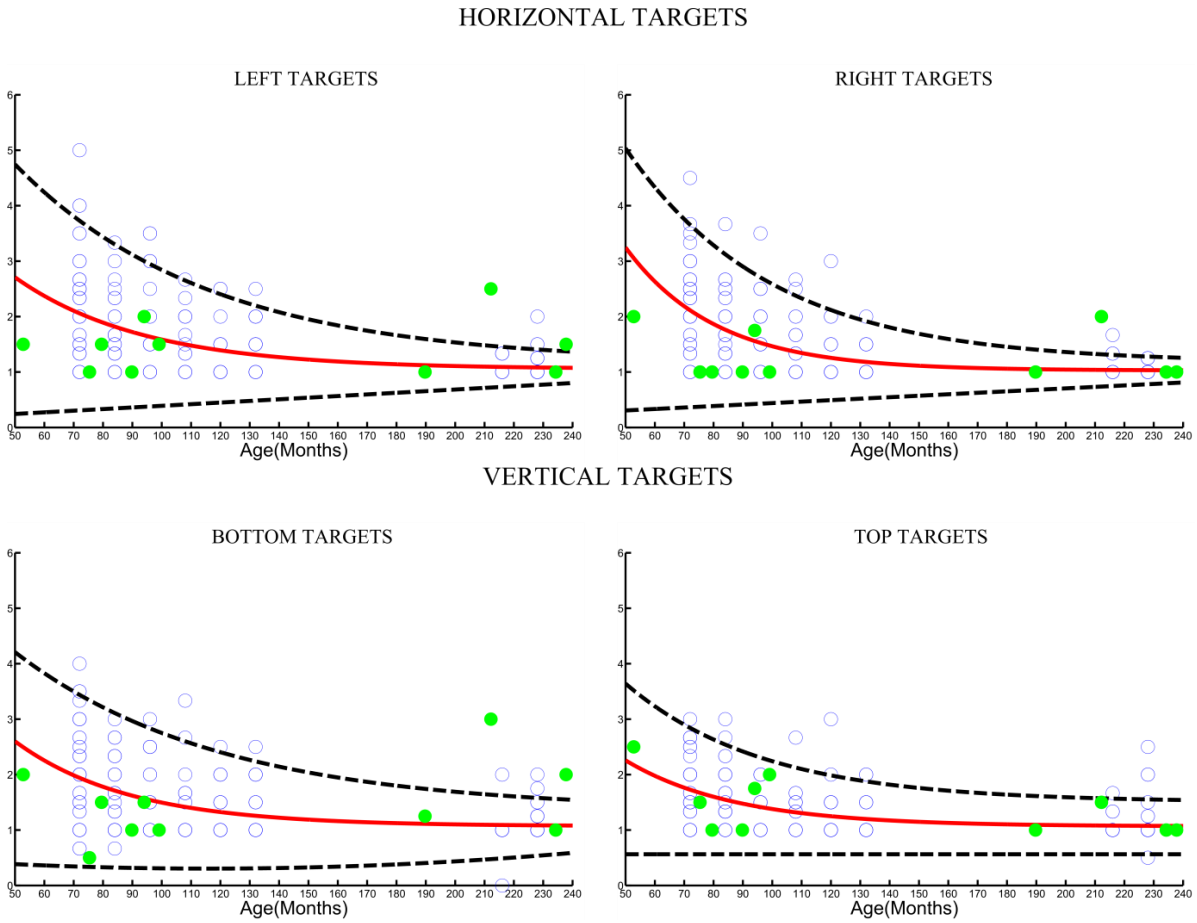


Figure 6.2.10: T3 intrusive saccade frequency individual patient performance. Average number of saccades away from the visual stimulus (*FixSacc*) produced by T3 patients (green dots) and healthy controls (blue dots). The healthy developmental trajectory (red line) is expressed as a plateau function. 95% confidence limits (black dotted-line) are also presented.

Table 6.2.13: T3 z-scores for intrusive saccades (*FixSacc*)

PID	Age (Years)	Target Position				Avg
		Left	*Right*	*Bottom*	*Top*	
1	4.4	1.50 (0.92)	2.00 (0.75)	2.00 (0.46)	2.50 (-0.48)	2.00 (0.61)
3	6.28	1.00 (1.16)	1.00 (1.21)	0.50 (1.75)	1.50 (0.30)	1.00 (1.50)
4	6.62	1.50 (0.50)	1.00 (1.15)	1.50 (0.39)	1.00 (1.14)	1.25 (1.01)
5	7.48	1.00 (1.04)	1.00 (1.02)	1.00 (0.93)	1.00 (1.02)	1.00 (1.38)
6	7.84	2.00 (-0.49)	1.75 (-0.31)	1.50 (0.10)	1.75 (-0.68)	1.75 (-0.45)
7	8.26	1.50 (0.16)	1.00 (0.90)	1.00 (0.83)	2.00 (-1.38) *	1.38 (0.30)
8	15.81	1.00 (0.51)	1.00 (0.27)	1.25 (-0.43)	1.00 (0.35)	1.06 (0.20)
9	17.68	2.50 (-7.31) **	2.00 (-6.71) **	3.00 (-6.88) **	1.50 (-1.67) **	2.25 (-8.89) **
10	19.52	1.00 (0.52)	1.00 (0.27)	1.00 (0.31)	1.00 (0.28)	1.00 (0.51)
11	19.82	1.50 (-2.79) **	1.00 (0.28)	2.00 (-3.84) **	1.00 (0.28)	1.38 (-2.70) **

Note: z-scores in parentheses ; * *z-score > 1*, ** *z-score > 2*

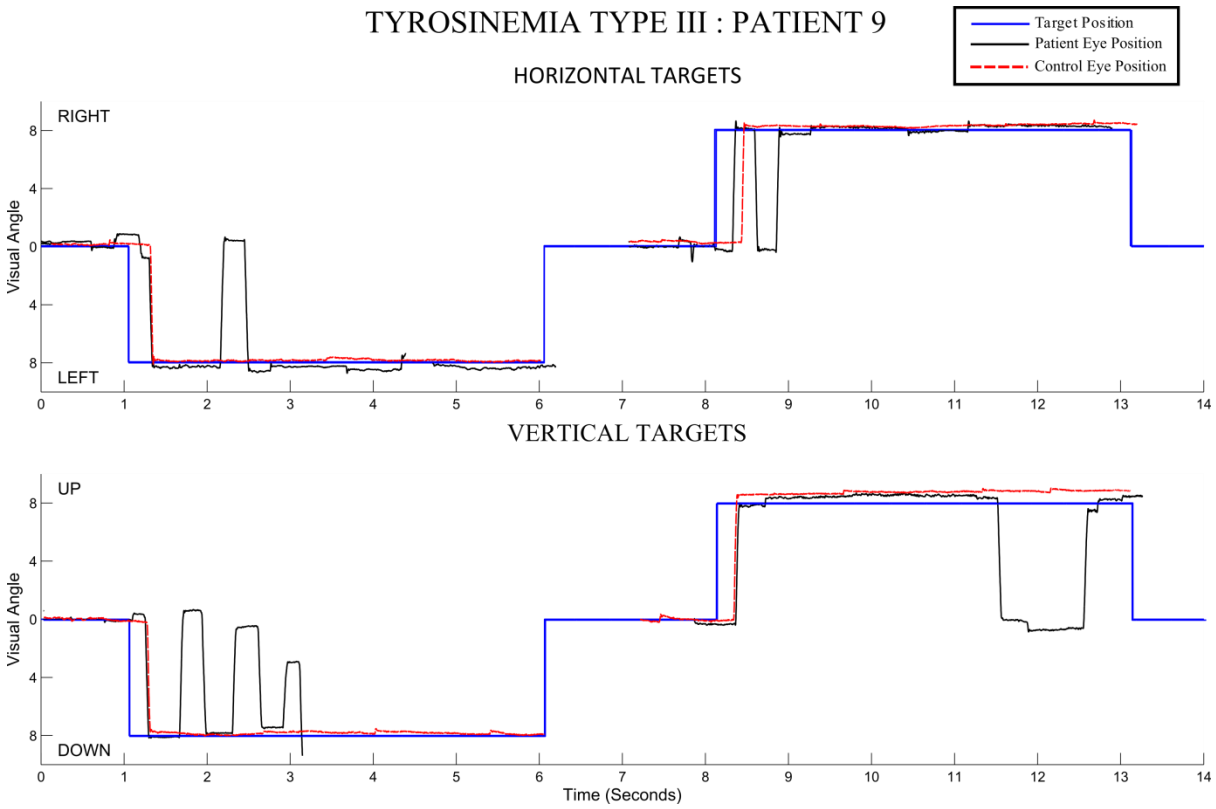


Figure 6.2.11: T3 fixation task raw temporal data. Time course data of T3 patient 9 during the fixation task. The visual stimulus (blue line) is presented along with patient (black line) and age-matched control eye position (dashed red line).

Finally, the AIC comparisons of T3 patient and control developmental trajectories for intrusive saccade frequency revealed there was insufficient evidence of 3- and 2-way interactions, and main effects, for *Group*, *SetSize*, and *Age*. This means there were no differences between the developmental trajectories of T3 patients and controls for intrusive saccade frequency.

6.2.4 Conclusions: Tyrosinemia III (T3)

The cognitive functioning of 11 tyrosinemia III (T3) patients was investigated using detailed cognitive measures of attention, language, and oculomotor function. In general, language production (*BNT*) and comprehension (*BPVS*) deficits were clear, with 6 / 10 (55%) and 8 / 11 (73%) patients exhibiting deficits respectively. These deficits were most apparent in the older T3 patients. Attention deficits were also evident, and were characterised by slower overall visual search time (*VSmean*) and lower sustained fixation durations (*FixDwell*) in 5 / 11 (45%) and 4 / 11 (36%) patients respectively. Here, the deficits were present in the youngest and eldest patients.

To our knowledge, this study represents the first detailed cognitive assessment of T3 patients, and highlights the predominance of language and attention impairments that are expressed by the group. The current findings support the previous T3 case reports by Ellaway et al. (2001), who reported mild to moderate intellectual impairments in a sample of 12 patients. However, these findings were based on case reports, and were unable to provide specific information about the kinds of cognitive deficits patients exhibited. The prevalence of T3 language deficits is also interesting since this is a frequently reported cognitive feature of NTBC treated T1 patients (Bendadi et al., 2014b; Thimm et al., 2011). This is because NTBC treatment biochemically switches T1 patients into T3 patients. Consequently, this finding provides indirect evidence that long-term NTBC treated T1 patients share similar cognitive features with T3 patients.

Treatment of T3 involves a strict tyrosine restricted diet, which is important for controlling patient's levels of tyrosine. Elevated levels of central nervous system tyrosine levels are particularly damaging during the first year of life. This was demonstrated by Ellaway et al. (2001), whereby patients who were diagnosed and treated later presented with more severe symptoms. In the current study, biochemically data such as tyrosine levels at the

time of diagnosis or compliance with diet were not measured. Hence, it is possible that the heterogeneous cognitive profile of patients on some tasks (e.g. visual search and fixation tasks) could result from differing diet start times between patients. To clarify these speculations, the effect of diet start time on cognitive outcomes is currently being explored in a separate project.

6.3 Chapter Conclusions

In this chapter, the cognitive performance of tyrosinemia type I and type III patients was examined on the current test battery. Tyrosinemia type I is a metabolic disorder that has received a relatively large amount of neuropsychological study (compared to other metabolic disorders) since long term treatment with NTBC is expected to produce cognitive impairments. In contrast, Tyrosinemia type III has enjoyed minimal attention, due to the rarity of the disorder, but has been associated with mental retardation based on a small number of case reports (Ellaway et al., 2001). Here, we reported a broad range of cognitive impairments in tyrosinemia III and mild deficits for a limited number of cognitive domains in tyrosinemia type I. In addition, we demonstrated some similarities between these two disorders in the form of disrupted language function. However, due to the small size of the tyrosinemia type I sample it was not possible to conduct a robust statistical comparison between the groups. Finally, there was large heterogeneity between tyrosinemia III patients on the current test battery. Specifically, cognitive deficits were more common among the youngest and eldest patients within the current cohort. In conclusion, two recommendations are offered for future research: First, studies should focus on integrating biochemical data into the cognitive assessment of these disorders to assist the interpretation of cognitive outcomes. Second, a comparison of a larger population of tyrosinemia I patients and tyrosinemia III patients to clarify whether NTBC treatment produces deficits in tyrosinemia I that mirror the deficits reported in tyrosinemia III.

7.0 CONCLUSION AND FUTURE DIRECTIONS

7.1 Conclusions

The current thesis aimed to create a new battery of neuropsychological tests that were tailored specifically towards measuring the neurodegenerative effects of inherited metabolic diseases (IMDs). These are a large group of complex heterogeneous genetic disorders that have received minimal attention from the field of neuropsychology. This is primarily due to the rarity of the disorders and because, understandably, the drive of past research has focused on improving the survivability of patients. With the advent of treatments (such as HSCT and ERT) that positively influence neuropsychological outcomes, there is a need for sensitive and objective neuropsychological measures that allow patients to be systematically tracked in order to understand the efficacy of these treatments. In addition, existing descriptions of cognitive function in children with IMD have relied predominantly upon standardised intelligence tests (Davison et al., 2012; Ellaway et al., 2001; Thimm et al., 2011), which are better suited to providing an overall measure of cognitive function. Hence, neurodegenerative effects of IMD on specific cognitive domains are not always clear.

The following demands necessitated the development of the current test battery: the clinical need for an instrument that can be used to accurately track disease progression; an objective and sensitive tool to evaluate positive and negative outcomes of therapeutic interventions; the research need for information on the specific impact of the neurodevelopmental disorders on language, motor control and attention. To determine whether the current battery of tests achieved these objectives, evidence gathered during the research is described here in the context of the following principle questions:

(i) What are the best measures (most sensitive and efficient) to use to track disease progression during different stages of the disease?

(ii) Do some cognitive domains develop/decline differently along the time course of a disease?

(iii) What is the homogeneity across and within diseases for the cognitive areas that are most and least affected by disease?

(i) *What are the best measures (most sensitive and efficient) to use to track disease progression during different stages of the disease?*

The cognitive functioning of IMD patients was evaluated across three cognitive domains: attention, language and oculomotor function. A summary of cognitive deficits for each of the five disorders that were assessed is shown in Table 7.1. Measures of attention (visual search and fixation tasks) were highly sensitive to the effects of IMD across a wide range of ages. This was demonstrated in several patient groups and was particularly evident amongst two lysosomal storage disorders, Hurler syndrome and Morquio syndrome. Here, prominent sustained fixation deficits were observed across the entire age range in both groups. Deficits of overall search time on the visual search task were also observed; however, for Morquio syndrome the magnitude of visual search deficits were smaller than those reported in the fixation task. Due to their sensitivity over a wide range of ages, the attention tasks used here provide a means of tracking IMD disease progression over a long-term time scale.

Table 7.1.1: Summary of cognitive deficits across disorders and cognitive domains

		Lysosomal Storage Disorders			Tyrosinemia Disorders	
Domain	Task	MPS-IH	MPS-IVa	MPS-VI	Tyro I	Tyro III
Attention	Simple RT Task	*	*	-	-	*
	Visual Search Task	**	**	-	-	*
Language	BNT	*	-	-	-	**
	BPVS	**	*	*	*	**
	Non-Word Task	**	-	-	*	*
Ocular Motor	Fixation Task	**	**	-	-	*
	Prosaccade Task	-	-	-	*	-
	Antisaccade Task	*	*	-	-	-
	Smooth Pursuit	-	-	-	-	-

Note: * possible deficit, ** *Consistent deficit*

Language tasks offered valuable insights into the neuropsychological profile of tyrosinemia diseases. Unlike attention tasks, where deficits were detectable across a wide range of ages, verbal production and comprehension tasks (BPVS and BNT) were most sensitive to impairments exhibited by older patients. In contrast, very few language impairments were detected by the novel non-word learning task. This was primarily due to the large variance exhibited by healthy controls for non-word production (which may have masked any subtle non-word production deficits that patients may have possessed) and the insensitivity of non-word comprehension to mild deficits (ceiling effect). As a result, in its present form, the non-word learning task is only sensitive to severe non-word learning

deficits. This means that, without revision, the functionality of the non-word learning task as a disease tracking tool is unacceptable.

Basic eye movement measures (pro-saccade and smooth pursuit tasks) were normal in almost all patients from the current patient cohorts. For the pro-saccade task, the normal range of saccadic onset latencies expressed by healthy controls was very narrow, so the absence of deficits here was not due to large control variance concealing milder patient deficits. Despite this, properties of reflexive saccades (saccade onset and velocity) were informative when exploring the underpinning of sustained fixation deficits; fixation duration deficits, as seen in Morquio patients, were not the consequence of patients' gaze arriving at the target later than controls. Finally, no smooth pursuit deficits, neither for velocity gain or forward saccade frequency, were identified in any patient. In summary, while the basic properties of eye movements have been shown to be disrupted in other IMDs (e.g. Niemann-Pick type C and Gaucher's disease; (Patterson et al., 2010; Vanier, 2013)), the current pro-saccade and smooth pursuit findings suggest that the basic properties of eye movements are not useful measures for tracking the progression of disease of the current cohorts. However, these results do serve as a useful comparison to tasks where patient performance is clearly disrupted (e.g. sustain fixation).

(ii) *Do some cognitive domains develop/decline differently along the time course of a disease?*

The AIC trajectory methodology employed here provided a rich descriptive approach towards evaluating any developmental differences that exist between patients and healthy

controls. Specifically, this approach enabled the distinction between different types of developmental deviation, such as whether trajectories of patients were offset or had a slower rate of development relative to healthy controls. By extension, this procedure permits the examination of how the cognitive development of patient groups differed across domains. For example in tyrosinemia III, simple reaction time development followed a normal developmental trajectory (both in terms of the rate and onset of development), while for verbal production and comprehension the development rate of patients was slowed in comparison to healthy controls, leading to the majority of older patients performed well below the predicted range of healthy development.

Detailed descriptions of patient cognitive development have several important clinical implications. Firstly, patient developmental trajectories provide an estimate of future patient performance. This is useful when evaluating the efficacy of novel therapeutic interventions, since cognitive outcomes can be compared against performance estimates that are independent of therapeutic effects, thus providing a more detailed description of treatment outcomes. Secondly, understanding how developmental trajectories differ across domains enables researchers and clinicians to choose the best age-appropriate measures to monitor cognitive outcomes. For example, in tyrosinemia III, language measures may serve as a meaningful outcome for older patients only. Finally, having representations of both patient and healthy development enables the tracking of individual patients against two developmental populations. In this way it is possible to describe how patients deviate (or do not deviate) from developmental trajectories representing their disorder and healthy developing controls.

However, patient developmental trajectories here are based on the cross-sectional analysis of rare populations. Consequently, caution is required when interpreting trajectories based on a limited number data points. This is especially relevant for trajectories representing

development in patients from a group where performance is heterogeneous. Therefore, it would be advantageous to have longitudinal data to characterise the variability of individual patient profiles that contribute to population trajectories.

(iii) *What is the homogeneity across and within diseases for the cognitive areas that are most and least affected by disease?*

The heterogeneous nature of IMDs, both across and within IMD, was clearly characterised within the current work. This was demonstrated through the comparison of individual patient z-scores to trajectories of healthy cognitive development, and the distribution of patient residuals around trajectories defined by the patient group. A clear example where heterogeneity was shown across disorders was for the three assessed lysosomal disorders. Here, three distinct cognitive profiles were identified; Hurler syndrome and Morquio syndrome patients exhibited severe and mild attention deficits respectively, while, Maroteaux-Lamy syndrome patients were normal on nearly all tasks. These findings were congruent with previous studies which investigated the functioning of these three disorders independently (Davison et al., 2012; Elkin et al., 2006; Neufeld & Muenzer, 2001; Wraith, 2006). This provides support for the use of the current test battery as a sensitive tool to assess the cognitive functioning of multiple neurodegenerative disorders with varying cognitive profiles.

The within-group heterogeneity that is associated with many IMDs was characterised by the performance of Morquio syndrome patients. By examining size of patient residuals around their constructed developmental trajectories, it is possible to ascertain the conformity of patients to a predictable developmental trajectory. In particular, there was substantial variance between patients on the visual search task, with a few patients exhibiting extreme deficits and the remainder being within the range of healthy development. In contrast, the

within-group heterogeneity of Morquio syndrome patients on verbal production and comprehension measures was minimal; all patients fell within (or just outside) the range the healthy development. Thus, the within-group heterogeneous variance that patients expressed across different cognitive domains was captured by the current test battery. Because heterogeneity within and across diseases was demonstrated in many of the investigated diseases, it will be important that biochemical data (e.g. metabolite levels) is integrated into future cognitive assessments to understand whether the heterogeneity in cognitive results is connected to specific biochemical factors (e.g. generally high toxic metabolite levels or periods of crisis).

7.2 Recommendation and Future Directions

Based on the evidence gathered over the course of the research, the following four recommendations are offered to researchers and clinicians who are interested in examining the cognitive effects of metabolic disease:

(i) Use of biological markers to supplement interpretations of cognitive outcomes

(ii) Alternative analysis methods: Longitudinal tracking and Contrast group designs

(iii) Inclusion of additional/alterative cognitive measures and assessment of other IMDs

(i) *Use of biological markers to supplement interpretations of cognitive outcomes*

As already stated, the heterogeneous nature (both within and across disorders) of IMDs means that in order to provide clearer descriptions of the neurological complications, there is a need for future research to incorporate sources of biological and biographical data in the interpretation of cognitive outcomes. For example, patients with tyrosinemia III are

treated with a restricted protein diet to manage their levels of tyrosine. Hence, the large variance demonstrated between tyrosinemia III patients on measures of attention (visual search and fixation tasks) could be the result of the more severely affected patients having higher levels of tyrosine present in their CSF. At younger ages elevated tyrosine levels could result from a later diagnosis, and at older ages, higher tyrosine levels could be due to poorer diet compliance. In addition, it could be possible that the protein restricted diet that tyrosinemia III patients are place presents additional risks to cognitive function.

Another possible avenue to explore is the correlation between neuroimaging findings and cognitive outcomes. To some extent, several studies have already utilised imaging techniques, such as magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and diffusion tension imaging (DTI), in the analysis of cognitive outcomes. For example, in the assessment of Morquio syndrome cognitive function by Davison et al. (2012), MRS findings revealed a negative correlation between white matter toxic metabolite concentrations and cognitive indices. In another example, Shapiro et al. (2012) found that Hurler syndrome patients who had lower attention spans also had decreased fractional anisotropy, as measured through DTI. Both studies highlight the importance of imaging techniques when interpreting the heterogeneity of patients' cognitive outcomes. The majority of studies, to date, have inspected the structural properties of patient brains in relation to cognition. It is reasonable for one future approach to also examine the functional properties of patient brains. This would provide additional spatial and temporal information about brain function (allowing inspection of where and when information is processed in the brain) and could be accomplished through function magnetic imaging (fMRI) or electroencephalography (EEG).

(ii) *Alternative analysis methods: Longitudinal tracking and Contrast group designs.*

A cross-sectional approach was taken to defining the developmental effects of rare IMD. While this approach has the advantage of being more time-efficient and places less burden on participating patients, the rarity of the investigated diseases means that estimates of development are based on a limited number of data points. Consequently, caution is advised when interpreting development based on the current findings, especially for purpose of clinical decisions. Because of the rarity of these disorders, future research should consider longitudinal follow-up to compliment a cross-sectional approach.

Another benefit of a longitudinal approach is the ability to inspect the heterogeneity of individual patient trajectories in relation to their respective population trajectory. This is important developmental information that a cross-sectional approach cannot provide. Therefore, it is not clear whether the population trajectories defined in the current work accurately reflect the trajectories of individual patients over time. For example, there might be considerable heterogeneity in the slopes of individuals that contribute to the population slope, which would mean that the rate of development is heterogeneous, or there could be different offsets in different patients, determined by severity, but a similar rate of development in individual patients.

An alternative approach to comparing patient performance with developmental trajectories is to compare patient performance to two typically developing contrast groups: a chronological age-matched (CA) group and a mental age-matched (MA) group. The objective of this approach is to determine whether individuals, or a group of individuals, from a disorder group possess impairments that are characteristic of developmental delay (i.e. patient performance differences only to the CA-matched group) or whether patients exhibit developmental deviance or atypicalilty (i.e. patient performance differs from both CA and MA-matched groups). Group comparisons using *t*-test or analysis of variance are the most

common statistical methods employed. Consequentially, matched design comparisons may be ill suited to investigations where groups occupy a wide age range, since group means may mask a wide range of individual performances. This poses a problem when investigating rare neurodegenerative disorders (such as IMDs) as these patient populations inevitably occupy a wide age range. In addition, to perform matching correctly it is important that the performance of the CA-matched and MA-matched groups is within the sensitive range of the employed task. Therefore, establishing an appropriate MA-matched group may not be possible when investigating disorder groups where severe learning difficulties are present.

A solution which combines the developmental trajectory and matched design approach may be adopted that provides a description of developmental delay and deviation without the need for a MA-matched typically developing contrast group (Thomas et al., 2009). This is achieved by first assessing the performance of a disorder group on an experimentl task (e.g. non-word learning) that relates to a cognitive domain of interest (e.g. language). In addition, data is collected on a further task that yields MA-equivalent performance levels for typically developing children. A typically developing comparison group is then recruited that spans from the youngest MA to the oldest CA of the disorder group, and the performance of these comparison individuals is assessed on the experimental task. Based on these data, patient performance can be compared to a typically developing trajectory to calculate two standardised scores: a z-score based on patient CA (as performed in the current work) where deviations could be indicative of developmental delay, and a z-score based on patient MA where deviations are suggestive developmetal deviance. However, for this approach to be performed correctly it is important that an individual patient MA-equivalent score are calculated for each of the cognitive domains under examination. This presents a problem when examining patients with servere learning disabilities on batteries of

neuropsychological tests since it may be unfeasiable to collect the necessary MA-equivalent scores within time that the patients are compliant with testing.

(iii) *Inclusion of additional/alternative cognitive measures and assessment of other IMDs*

Cognitive functioning was assessed on three domains. While attention and language tasks were sensitive to mild cognitive impairments, many of the oculomotor tasks were not. There might be several reasons for this: First, the difficulty of the anti-saccade task was too high, which meant establishing a sensitive measure that captured the healthy development of saccadic inhibition was not possible. Therefore, future studies intending to assess saccadic inhibition should use a task with less demanding testing conditions. For example, a simplier memory-guided saccade task would provide a measure of saccadic inhibition and data based on the basic properties of endogenous saccadic eye-movements (e.g. saccade onset and velocity). Second, the neurodegenerative effects of the investigated diseases did not manifest in the reflexive properties of saccades and smooth pursuit. However, it is recommended that the inclusion of these tasks is preserved since the saccadic system has been shown to be clearly compromised in other IMDs (Niemann-Pick Type C and Gaucher disease; Vanier, 2013; Wraith et al., 2010) and they are informative when interpreting outcomes of other eye-movement measures.

An additional measure which researchers may consider adopting into the test battery is a measure of postural sway or gait stability. This is because ataxia is a commonly reported symptom in several IMDs, such as tyrosinemia III, Niemann-Pick Type C, and Gaucher disease (Ellaway et al., 2001; Paciorkowski et al., 2008; Wraith et al., 2010). In particular, upper limb tremor and gait instability in Niemann-Pick type C patients has been documented in two studies (Floyd et al., 2007; Paciorkowski et al., 2008). Here, kinematic measures

offered a means of capturing change in motor function over time, and a method to evaluate the efficacy of a new treatment (Miglustat). Therefore, a sensitive measure that is capable of quantifying the kinematics of postural sway and gait could compliment the current test battery.

7.3 Chapter Conclusions

The current body of work introduces new data and objective methods for studying the neuropsychological effects of IMDs. Findings from five patient cohorts indicated that disease effects were not homogeneous across tasks, and that performance on the same tasks was not uniform across diseases. Several measures that were sensitive to disease progression were identified that will provide clinicians and researchers with new tools to track how diseases affected cognitive function and quantify treatment benefits. In addition, the obtained data offers a promising basis for understanding how biochemical and biographical factors influence the severity and timecourse of developmental effects. Finally, the data also makes several clear extensions possible. This includes the correlation of cognitive performance to structural and functioncal brain changes by combining the current methods with data from brain imaging, and also, a fuller understanding of population and individual profiles is possible if these methods are used in longitudinal studies to understand the progression of development in individuals over time.

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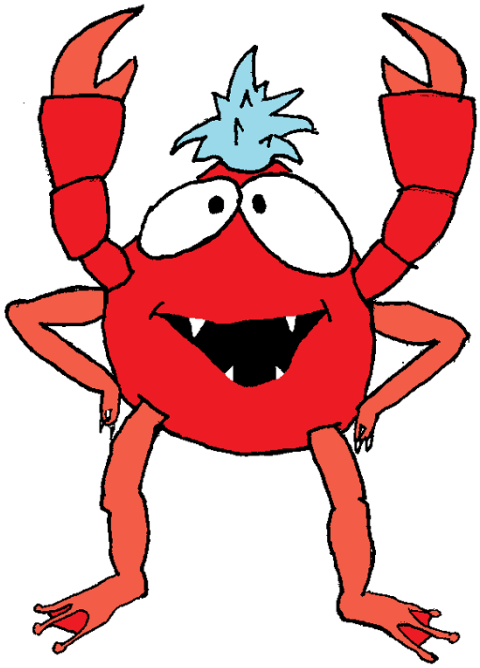
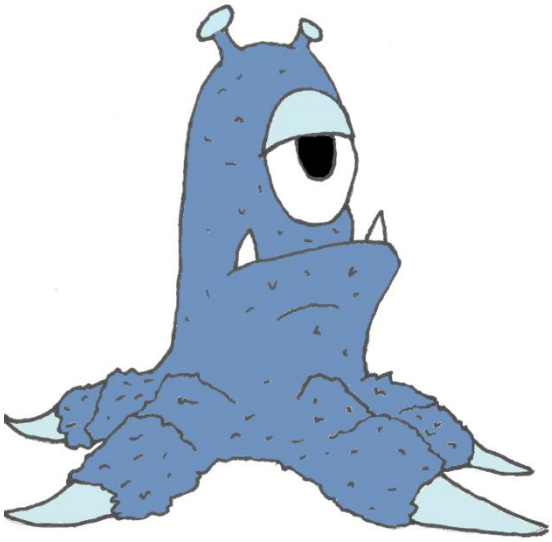
APPENDIX 1: Non-Word Learning Stimuli

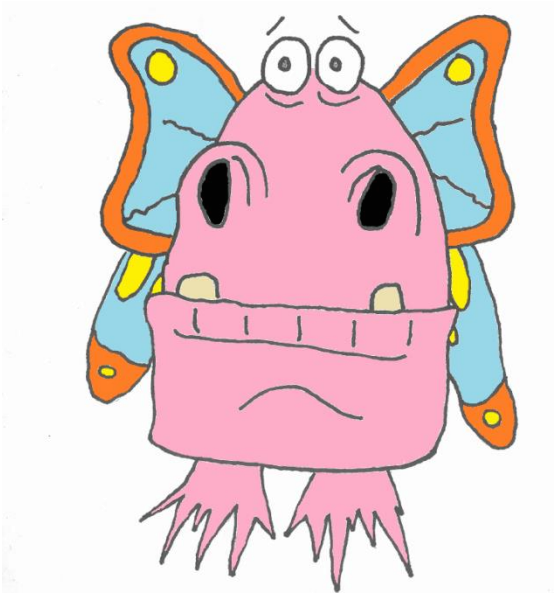
Images and related non-words used as the stimuli during the non-word task. All images were presented on laminated card (15 x 21cm). A 2-syllable non-word name was assigned at random to each monster at the beginning of the thesis. Names here are presented along with APA phonetic representation.



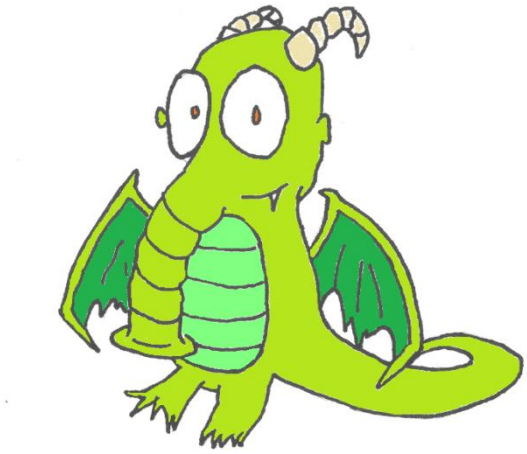
Nimack (*nimack*)



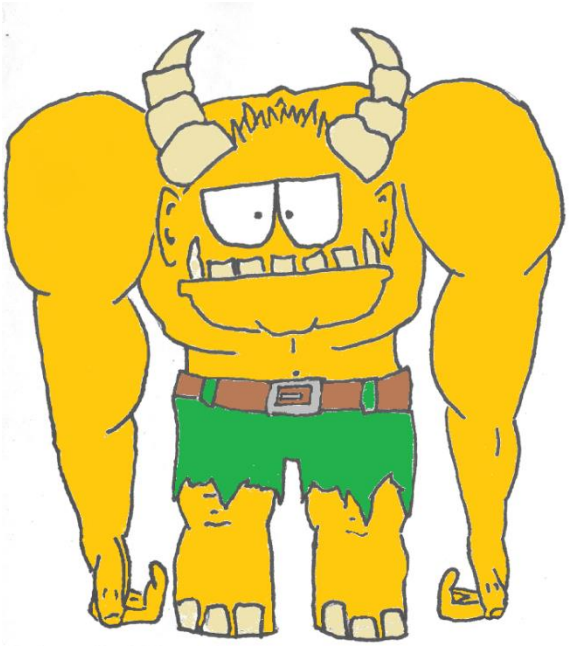
Vargan (*vargan*)



Jiplo (*yiplo*)



Teldom (*teldom*)



Gafnic (*gafnic*)