

Markers of cognitive function in patients with metabolic disease: Morquio Syndrome and Tyrosinemia Type III

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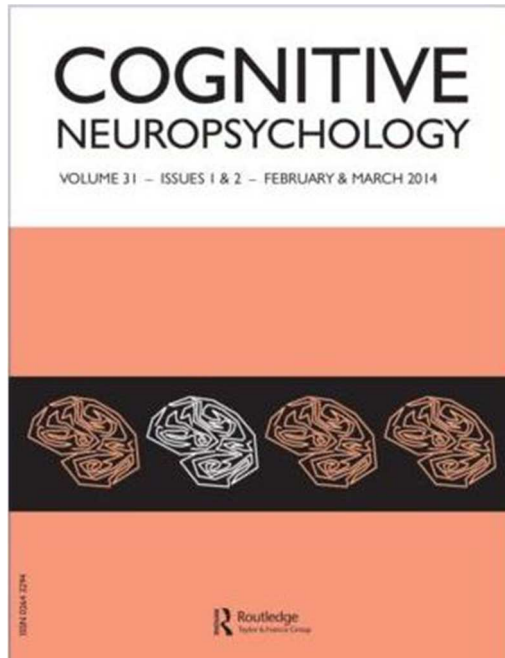
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Markers of cognitive function in patients with metabolic disease: Morquio Syndrome and Tyrosinemia Type III

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10 and Tyrosinemia Type III
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Abstract

We characterised cognitive function in two metabolic diseases. MPS-IVa (Morquio) and Tyrosinemia Type III individuals were assessed using tasks of attention, language and oculomotor function. MPS-IVa individuals were slower in visual search, but the display size effects were normal and slowing was not due to long reaction times (ruling out slow item processing or distraction). Maintaining gaze in an oculomotor task was difficult. Results implicated sustained attention and task initiation or response processing. Shifting attention, accumulating evidence and selecting targets were unaffected. Visual search was also slowed in Tyrosinemia Type III and patterns in visual search and fixation tasks pointed to sustained attention impairments, although there were differences from MPS-IVa. Language was impaired in Tyrosinemia Type III but not MPS-IVa. Metabolic diseases produced selective cognitive effects. Our results, incorporating new methods for developmental data and model selection, illustrate how cognitive data can contribute to understanding function in biochemical brain systems.

Keywords: Morquio, MPS-IVa, Tyrosinemia, inherited metabolic disease, language, attention, developmental disorder

Markers of cognitive function in individuals with mild metabolic disease: Morquio
Syndrome and Tyrosinemia Type III

Inherited metabolic diseases (IMDs) are large and heterogeneous class of genetic disorders that are caused by dysfunction within a single pathway of intermediary metabolism. In these diseases the dysfunction of metabolic enzymes leads to the accumulation of metabolites, which are often toxic, disrupting the normal development of multiple systems. 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, 2013; Wraith, 2006). Severe consequences include mental retardation, central nervous system (CNS) complications, and reduced life expectancy (Bendadi et al., 2014; De Laet et al., 2011; Masurel-Paulet et al., 2008; Thimm et al., 2011, 2012). Research into the cognitive impact of IMDs has largely been limited to standardised intelligence tests, achievement tests and adaptive behaviour scales (Bax & Colville, 1995; Biernacka, Jakubowska-Winecka, & Tylki-Szymanska, 2010; Davison et al., 2013; Shapiro et al., 2009). These do not generally allow impairments in specific cognitive domains to be characterised or tracked over time (Martin et al., 2008). In the current study we present results from two IMD groups, Morquio syndrome and Tyrosinemia type III, where cognitive impairments have been considered mild (using standardised tests). We compare individuals with Morquio syndrome and Tyrosinemia type III to typically developing controls (Thomas, Annaz, & Ansari, 2009) to evaluate affected and preserved cognitive abilities in the domains of language, attention and oculomotor control.

Morquio Syndrome (MPS-IVa , OMIM 253000)

Morquio syndrome (MPS-IVa) is lysosomal storage disorder that is caused by the deficiency of the lysosomal enzyme N-acetylgalactosamine-6-sulfase (GALNS, EC 3.1.6.4; encoded by GALNS gene at 16q24.3) which has a role in degradation of the glycosaminoglycans (GAG) keratan sulphate and chondroitin-6-sulfate (Neufeld & Muenzer, 2001; Wraith, 2006). Both keratan sulphate and chondroitin-6-sulfate are essential constituents of connective tissue, including cartilage and vessel walls. The accumulation of these two GAGs leads to a classic phenotype defined by severe skeletal dysplasia, hip dysplasia, marked short stature, genu valgum, and cornea clouding (Hendriksz et al.,

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3 2013; Wraith, 2006). Treatments to reduce substrate burden in MPS-IVa include enzyme replacement
4 therapy (ERT) and haematopoietic stem cell transplantation (HSCT), which alleviate the majority of the
5 skeletal and coronary complications.
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9 In contrast to other lysosomal storage disorders (e.g. Hurler-Scheie syndrome, Hunter's
10 syndrome, Niemann-Pick Type C), Individuals with MPS-IVa have not typically been reported to have
11 neurological or neurocognitive impairments (Dvorak-Ewell et al., 2010; Wraith, 2006) and
12 neuroimaging results usually find no neuroanatomical abnormalities (Koto, Horwitz, Suzuki, Tiffany, &
13 Suzuki, 1978). However, recent neurocognitive findings (Davison et al., 2013) from eight individuals
14 with MPS-IVa (aged 5 -17 years) suggested that mild/borderline cognitive impairments do exist. Age
15 appropriate standardised tests (e.g. WASI, WISC) revealed full scale IQ scores either in the lower
16 average range (80 – 90), borderline range (70 – 80), or extreme low range (<70) in four individuals. The
17 remaining four individuals had normal Full Scale IQ (85 – 115). Attention problems were reported by
18 the majority of parents using the Child Behavioural Checklist.
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29 Mild cognitive impairments were supported by MRS findings in the same study. In three
30 individuals with cognitive impairments there was a correlation between white matter metabolite
31 concentrations (N-acetylaspartate) and cognitive indices. In addition, MRI findings revealed
32 neuroanatomical abnormalities in more than half the MPS-IVa individuals. These included mild
33 asymmetry of the lateral ventricles, prominent perivascular spaces and high signal white matter areas of
34 the right frontal lobe. Unlike the MRS findings, there was no correlation with cognitive indices, but
35 this could be because the behavioural measures lacked sensitivity. A formal assessment of attention is
36 needed, especially in the context of the attentional difficulties reported by parents.
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44 **Tyrosinemia Type III (T3, OMIM 276710)**

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46 Tyrosine is an amino acid that is catabolised into fumarate and acetoacetate, both of which are
47 important for gluconeogenesis and ketogenesis. Dysfunction at different points in this enzymatic
48 pathway will lead to one of three identified hypertyrosinemia disorders: tyrosinemia types I to III,
49 which result in the accumulation of plasma tyrosine levels and increased urine excretion of tyrosine
50 (Chakrapani, Gissen, & Mckiernan, 2012). Tyrosinemia type I is caused by a deficiency in
51 fumarylacetoacetate hydrolase, the final enzyme in the tyrosine catabolic pathway. It leads to an
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3 accumulation of highly toxic fumaryl- and maleylacetoacetate in the liver. This produces organ
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5 dysfunction and carcinogenesis, with hepatocellular carcinoma a frequent cause of death in childhood.
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7 Tyrosinemia type II, results from a defect in tyrosine transaminase, the first enzyme in the tyrosine
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9 pathway. It affects the eyes and skin, but also mental development. Tyrosinemia type III (T3), the
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11 disease we are concerned with here, is caused by the deficiency of 4-hydroxyphenylpyruvate
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13 dioxygenase, the second enzyme in the pathway. It causes extreme accumulation and increased
14
15 excretion of tyrosine, but not the increase in the toxic metabolites associated with the later type I
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17 enzyme defect (Chakrapani et al., 2012; Scott, 2006). Treatment consists of a low-protein diet and
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19 administration of ascorbic acid to control tyrosine levels (Scott, 2006).

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21 T3 is the rarest of the three tyrosinemias and the effects of elevated concentrations of tyrosine in
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23 the central nervous system are not well established. Only 15 cases have been reported in the literature to
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25 date (Ellaway et al., 2001; Heylen et al., 2012; Szymanska et al., 2015). However, neurological and
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27 intellectual difficulties are commonly reported. Ellaway et al.'s (2001) review is the best description of
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29 cognitive functioning in 13 T3 individuals. Eight had neurological symptoms, such as developmental
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31 delay or mental retardation, attention deficit and behavioural disturbances, acute ataxia, tremor,
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33 hypotonia and absent deep tendon reflexes. The most common long-term complication was intellectual
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35 impairment (75% of individuals; Ellaway et al., 2001). Ellaway et al. speculated that the intellectual
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37 impairments resulted from the neurotoxic effects of elevated tyrosine levels. Their results, however,
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39 were based on aggregated scores (e.g. e.g. Stanford-Binet, WISC, WASI), so a profile of specific
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41 cognitive impairments remains to be determined.

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43 Tyrosinemia type I is treated with 2-nitro-4-trifluoromethylbenzoyl (NTBC), which makes treated
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45 type I an indirect window on T3. Treatment stops tyrosine metabolism earlier and prevents the
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47 accumulation of toxic metabolites that cause liver cancer, but it also gives T1 individuals the same
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49 biochemical profile as T3, raising tyrosine concentrations. T1 is a more common form of tyrosinemia
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51 and, in contrast to T3, more detailed reports of neurocognitive function exist (Bendadi et al., 2014;
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53 Thimm et al., 2011; Van Ginkel et al., 2016) Different studies have documented lower IQ scores and
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55 specific language production and comprehension impairments in NTBC-treated T1 individuals
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57 (Bendadi et al., 2014; Thimm et al., 2012).

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3 The most detailed assessment of cognitive function in T1 was recently reported by Van Ginkel et
4 al. (2016), measuring nineteen NTBC-treated individuals with both age-appropriate psychometric tests
5 (e.g. WISC and WASI) and additional measures of executive functioning. Average IQ was lower
6 (median 85: range 55 – 111) and there were specific working memory deficits (in reaction time and
7 error rates). No differences in inhibition were found. The cognitive deficits from the T1/NTBC studies
8 could be due to elevated levels of neurotoxic tyrosine, but they could also be a direct effect of NTBC
9 (Van Ginkel et al., 2016). Results from T3 can help to clarify this.
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16 Taken together, these findings (Bendadi et al., 2014; Ellaway et al., 2001; Thimm et al., 2012; Van
17 Ginkel et al., 2016), give us some reason to predict cognitive impacts in tyrosinemia type III. As with
18 Morquio Syndrome, we will characterise the presence or absence of deficits across cognitive domains
19 (language, attention and ocular-motor control) to show whether there is a homogeneous pattern, or
20 selective deficits in particular areas.
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26 **Patterns associated with functional deficits**

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28 We probed the cognitive domains of attention, language and oculomotor control to see if deficits
29 selectively affect different domains in different diseases. Beyond this, some deficits predict
30 characteristic patterns across domains. We distinguish deficits in processing speed, selective attention,
31 sustained attention.
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36 A deficit of *processing speed* should be particularly evident in a simple RT task, where cognitive
37 demands are minimized, allowing speed to be a primary influence on outcomes, but effects should be
38 noted in all speed dependent tasks, including conjunction and feature search and saccade onset times.
39 Slower processing speed should produce exaggerated effects of difficulty in tasks where the number of
40 operations is manipulated explicitly, like conjunction search. For the same reason, when dividing
41 reaction times into quintiles, slower reaction times should show larger differences from controls than
42 faster times, although there could be some difference even for faster times.
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50 A deficit of *selective attention* should impact conjunction search specifically, leading to increased
51 effects for larger displays, without changing feature search times, simple reaction time or saccade
52 onsets. Larger differences should be noted in slower quintiles of the RT distribution for conjunction
53 search only.
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3 A deficit of *sustained attention* should lead to shorter times on target in the fixation task and more
4 intrusive saccades. It should also create a subset of longer reaction times in search tasks (due to
5 distraction). Faster reaction times, however, should not be different from controls.
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10 **Methods**

11 **Participants**

12 *Morquio Syndrome (MPS IVa) and Tyrosinemia Type III (T3)*

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15 Thirteen individuals with MPS-IVa (8 male; mean age: 9.59 years, range: 5.27 – 14.39 years)
16 and eleven with tyrosinemia type III (3 male; mean age: 12.53 years, range: 4.40 – 19.58 years) were
17 recruited at Birmingham Children’s Hospital, UK (demographics in Appendix 1). Diagnosis of MPS-
18 IVa was confirmed via genetic testing. All MPS-IVa individuals had a severe phenotype of the disease,
19 but none had corneal clouding and none was ventilated. Tyrosinemia Type III was confirmed via
20 genetic testing after elevated tyrosine levels were detected during newborn screening. All individuals
21 were native English speakers. A number were bilingual (see Appendix 1). Both groups of children
22 with disease were tested in 2012-13 at the Wellcome Trust Clinical Research Facility at the
23 Birmingham Children’s Hospital. Consent was obtained from parents/guardians prior to testing.
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34 *Typically Developing Controls (TD)*

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36 Individuals with metabolic disease were compared to typically developing controls (TD), using
37 a developmental trajectory approach (e.g. Thomas et al., 2009). We tested a large sample of controls
38 across a range of ages between 6 and 20 to establish the trajectory of typical development in each
39 cognitive domain (Attention tasks $N = 104$, Language tasks $N = 104$, Oculomotor tasks $N = 265$). Prior
40 to testing, informed consent was taken from undergraduate student participants or from parents of child
41 participants.
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48 **Apparatus & Procedure**

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50 Our battery of test took approximately 1 – 1.5 hours to complete, depending on ability and need
51 for breaks.
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54 Attention and oculomotor tasks were created using Experiment Builder (SR Research Ltd.,
55 Mississauga, Ontario, Canada). Participants viewed stimuli from 60 cm on a 36 x 27 cm CRT-monitor
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3 with a resolution of 1024 by 768 pixels and a refresh rate of 60Hz, producing a viewing area of 33.5° x
4 25.5° (width x height) of visual angle. Reaction time (RT, measured in milliseconds, msec) for manual
5 responses were recorded using a Cedrus button box (<http://cedrus.com/>).
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9 Eye movements were recorded via an EyeLink® 1000 Tower Mount (SR Research Ltd.,
10 Ontario, Canada). Eye position was measured using corneal reflection via an infrared camera. Head
11 movement was minimized using a forehead and chin rest. Eye movements were calibrated to an
12 accuracy of at least 1° using a nine-point calibration array. Drift correction was employed before each
13 trial. Participants were recalibrated if central fixation was inaccurately displayed. Saccade detection was
14 based on default EyeLink 1000 settings (19-sample window): samples were classified as part of a
15 saccade if eye velocity exceeded 22°/second and eye position changed more than 0.3°, otherwise
16 samples were classified as fixations. Prior to analysis, trials from all tasks were visually inspected to
17 ensure that participants were engaged in the task and artefacts had been removed.
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27 **Attention tasks**

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29 Attention tasks included simple reaction time and visual search. We familiarised participants
30 with the visual search targets (red ladybirds) by introducing them in the simple reaction time task,
31 which was always presented first.
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35 Simple reaction time measured speed to respond to appearance of a visual target. Participants
36 completed 20 trials where a red ladybird (5.5° x 7.5°) was presented in a box in one of the four
37 quadrants around the centre (upper left, upper right, lower left, lower right; box size = 10° x 9°; 12°
38 diagonal distance from screen centre). Quadrants were systematically probed in this task and in the eye-
39 movement tasks because regions of space can be affected by attention or eye-movement deficits (e.g.
40 neglect, usually affecting attention to the left side of space, or vertical supranuclear gaze palsy, affecting
41 vertical eye-movements). The target appeared in each quadrant 5 times, with the order of the target
42 locations randomised between participants. Each trial began with a centrally presented fixation cross (1°
43 x 1°). After a variable delay of 1500–4000 ms the red ladybird target stimulus was presented in one of
44 the four quadrants. Participants were instructed to respond with their preferred hand, using a single
45 button press, as quickly as possible after the target appeared. The stimulus remained on the screen until
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3 the participant made a response or for 3000 ms. There was an inter-trial interval of 1000 ms prior to the
4 presentation of the fixation cross for the following trial.
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7 Visual search is a prototypical task of selective attention that has been studied
8 extensively and used to motivate a number of influential models (Bundesen, Habekost, & Kyllingsbæk,
9 2005; Moran, Zehetleitner, Muller, & Usher, 2013; Schwarz, 1993; Schwarz & Miller, 2016; A.
10 Treisman & Gelade, 1980; A. Treisman & Sato, 1990; Verghese, 2001; Ward & McClelland, 1989;
11 Wolfe, 2007). Our visual search task consisted of 3 feature search blocks and 3 conjunction search
12 blocks. In all blocks participants indicated, with a yes/no button press, whether the red ladybird
13 character was present. Feature search asked the participants to search for the red ladybird among a set of
14 green ladybird distracters. The target was defined by colour only. This means that the target typically
15 appears to “pop out” regardless of the number of distractors. Instead, conjunction search asked
16 participants to search for a red ladybird among green ladybirds and red beetle distractors. No single
17 feature dimension defines the target (it is red AND a ladybird) and this typically means that items need
18 to be searched more systematically, leading to longer reaction times for larger displays. Each block
19 contained 12 trials with 3 display sizes (4, 8, and 12 items). The target was present in half the trials in
20 each block. Block order was randomised between participants. Search displays were created by dividing
21 the screen into a 4 x 4 grid (each grid location = 8.5° x 6.5°). Search items (4° x 5° of visual angle) were
22 randomly assigned to the 16 grid locations. Each item’s position was jittered by a random amount to
23 make displays less regular (x maximum ±2° and y maximum ±1°). For target-present conjunction
24 trials one red beetle distractor was replaced with the target to ensure the number of red and green
25 elements were equal.
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44 Each trial began with a centrally presented fixation cross (1000 ms), followed by the stimulus.
45 Participants used a Cedrus button box to make a response (left button = target absent; right button =
46 target present). Stimuli disappeared after a response or if no response was registered within 10 seconds.
47 A blank screen was displayed (1000 ms) prior to the following trial. At the beginning of each block
48 participants were informed of the block type (feature or conjunction). Targets and distractors were
49 shown on screen and verbal instructions given by the experimenter. There were four practice trials with
50 feedback, at the beginning of the experiment, to familiarise participants with the task.
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3 We used response times for correct responses to calculate a mean visual search reaction time
4 (or intercept). We also measured search efficiency, defined as the slope of RT change with increasing
5 display size.
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8 9 **Language tasks**

10 Measures of verbal production (Boston Naming Task or BNT; Kaplan, 2000) and
11 comprehension (British Picture Vocabulary Scale or BPVS; Dunn et al., 1997) were used to assess
12 children's language abilities.
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16 The BNT is a 60-item picture naming test where items increase in difficulty, becoming
17 increasingly infrequent and unfamiliar (e.g. trellis). If a participant was unable to name an item, a
18 semantic cue was offered. A phonetic cue was provided if the semantic cue failed to produce a correct
19 response. An item was counted as correct if the participant was able to name it with or without a
20 semantic cue, and incorrect if the participant failed to produce the name or did so only after a phonetic
21 cue. The test is stopped if participants make more than 5 consecutive errors.
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28 The BPVS is a receptive vocabulary test. Participants listen to a word and select a matching
29 picture from four alternative line drawings. There is no spoken response. There were 14 sets of 12
30 items, which, like the BNT, increase in difficulty because the targets are increasingly uncommon items.
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35 The test was stopped if there were eight or more errors on a single set.
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37 **Oculomotor tasks**

38 Oculomotor function was tested using a fixation and pro-saccade task (Fischer & Weber, 2010;
39 Klein, 2001; Munoz & Everling, 2004; Salman et al., 2006).
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42 *Fixation Task*

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44 Participants were asked to fixate a central target, look to the target when it moved to one of four
45 possible non-central positions and then maintain their gaze until the target disappeared. There were 20
46 trials. An elephant face target (1.5° in size) appeared in the centre of the screen and then moved to a
47 location 10° to the left, right, above or below central fixation. Possible target locations were marked
48 with small circles (0.5° in size) to indicate where the target might appear. Trials began with the
49 presentation of the target centrally for 1000 ms. The target disappeared and immediately reappeared (no
50 gap or overlap) randomly at one of the four surrounding locations. The target remained at this location
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3 for 5000ms and participants were asked to maintain fixation on the target until it disappeared. A 3 x 3°
4 box surrounding each target was defined as a region of interest (ROI) and fixations within the ROI were
5 counted as fixations on the target. Dwell time was defined as the length of time participants maintained
6 eye position within the target's ROI (*FixDwell*). The frequency of intrusive saccades away from the
7 target (greater than 2°) that moved the participant's gaze outside the target ROI were also measured
8 (*FixSacc*).
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14 *Pro-saccade Task*

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16 Participants viewed 48 trials where a target elephant face (1.5° in size) randomly appeared at
17 one of eight positions around a central starting position. The four locations from the fixation task were
18 used (see above), along with four additional locations, closer to the centre (eccentricity = 5°). Each trial
19 began with the stimulus displayed at the centre of the screen for a random amount of time between 1000
20 and 2000ms. The stimulus then disappeared and reappeared at one of the possible target locations for
21 1000ms without any gap or overlap. Participants were asked to look as quickly and accurately as
22 possible directly at the target. There was no instruction to maintain fixation.
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30 To be included in the analysis, saccades had to start at the centre of the screen and the eye
31 movement had to be toward the peripheral target. We measured the onset of the first movement toward
32 the target and its peak velocity. To simplify the presentation only data from targets at 10°, where the
33 distance is greater, are presented here, but data from closer targets did not change the pattern.
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39 **Data Analysis**

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41 Across tasks, reaction times that were greater than 3 SDs away from individual participant
42 means were defined as outliers and removed. Individuals with metabolic disease and typically
43 developing (TD) control children were compared using a developmental trajectory approach (Thomas et
44 al., 2009). Developmental change was modelled as a linear or quadratic function of age. We were
45 interested in differences in the *rate* of developmental change (differences in the slope of trajectories)
46 and differences in absolute levels of performance (offsets between disease group and control
47 trajectories). Data from our experimental tasks was fit using linear mixed effects models (LME, using
48 the R package *lme4*) with fixed factors for *Group*, *Age* and, where appropriate, *Condition* (e.g. target
49 location). A main effect of *Group* indicated an effect of disease across all ages, and a main effect of *Age*
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3 indicated age-related developmental change. Interactions between *Group* and *Age* indicated that
4 disease modified the rate of developmental change. Akaike's Information Criterion (AIC) was used to
5 compare models (Burnham & Anderson, 2002).¹
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9 The set of models we compare are familiar from more traditional analyses (e.g. ANOVA). For
10 example, in an experiment with factors of *Age*, *Group* and *Condition*, we start from a model whose
11 most complex term is the three-way interaction *Age X Group X Condition* (this model will also contain
12 all lower-level two-way interactions and main effects). We compare this to the set of simpler models
13 that have one or more effects removed. If a simpler model accounts for data as well as a complex
14 model, the missing effects were not important. Our final model includes only effects that are needed to
15 account for the data. The highest order model for each analysis, the one reduced models are derived
16 from, is listed as the *generating model* along with models results in Appendix A. Random effects
17 structures for each analysis are also listed in Appendix A. The list of model results includes the models
18 closest to the minimum AIC model. Models not listed were worse.
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29 We report results from a large sample of controls and a much smaller sample of individuals
30 with metabolic disease, as is inevitable in the study of rare diseases. This means that models that do not
31 involve the *Group* term are largely determined by the data from normally developing control
32 participants. For each task, we initially model only data from typically developing controls to
33 characterise normal development (e.g. to ask whether the effect of *Age* is absent, linear or quadratic).
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41 ¹Model selection using AIC is different from p-values, but not difficult to understand. AIC is
42 preferred for model comparison because, unlike p-values, AIC balances fit and the number of model
43 parameters when choosing models. In brief, better models produce smaller AIC values, but the
44 absolute AIC values are not interpretable. Instead, the change in AIC (Δ AIC) between models is
45 meaningful and captures the weight of evidence for each model (rather than being subject to a cut-off,
46 like p-values). Evidence for a model starts to be clear if the Δ AIC exceeds 2. If Δ AIC between the
47 "best" model and alternative models is less than 2 then the two models are substantially equivalent.
48 When Δ AIC is between 2 and 10 there is decreasing support for an alternative model. A model with a
49 Δ AIC > 10 has essentially no support. For models where the Δ AIC is less than 2, it is reasonable to
50 favour the least complex model (i.e. model with fewest parameters/variables). Favoured models
51 contain terms that are important in accounting for data. This is parallel to significant effects in an
52 analysis using hypothesis testing. For example, if a highly-rated model has a term for *Group* but no
53 interaction, this is parallel to a significant main effect of *Group* and a non-significant interaction.

54 Comparisons can be assisted by calculating Akaike weights (AIC_w; Burnham & Anderson,
55 2002). AIC_w expresses the relative probability that a model is the best *in a particular set*, considering
56 only the models from that set. It measures the weight of evidence for the models being compared.
57 When values are relatively equal across two or more models, they are all relatively good models of the
58 data. If one model has a high value and the others are low, there is a model that is clearly better.
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Then, using the full dataset, we check interactions between terms in the best model for control data and *Group* (i.e. results from control and disease groups concentrate on evaluating the influence of the term for *Group*).

Because of possible heterogeneity among individuals within each disease group we also compared individuals with disease to typically developing controls (TD). The question was whether each individual was inside or outside the range of typically-developing values. To define the range of typically developing values, 95% prediction intervals were defined at each age, setting a cutoff above and below the TD means. Ninety-five percent of individual control values should fall between these points. Cutoffs for each age were smoothed to a boundary that applied across ages by fitting a curve, separately, to the set of upper boundary points and then lower boundary points. This minimises the impact of idiosyncratic estimates, smoothing the boundary position across ages by borrowing information from adjacent age groups. After defining limits, individuals with disease were compared to controls using the equivalent of z-scores, but using the upper or lower endpoints of the smoothed prediction intervals, rather than the noisier age-specific cutoffs. We label these z_{pi} .²

Results

Table 1 summarises domains where Morquio (MPS-IVa) and Tyrosinemia (T3) individuals had difficulties (shaded in grey) and is based on the results described in more detail below. The number of individuals who performed worse than the control mean, worse than 1 SD from the control mean and worse than 2 SD from the control mean are listed. MPS-IVa individuals displayed clear deficits in sustained attention and non-decision aspects of selective attention tasks, e.g. the amount of time fixation could be maintained and reaction time intercepts in visual search. T3 individuals exhibited clear deficits in language tasks (*BNT* and *BPVS*). They also had problems with sustained attention that affected fixation and visual search and modest slowing in simple reaction time.

Table 1 about here

² Specifically, for values above the mean, $SD_{pi} = (PI_{upper} - control\ mean)/1.96$ and $z_{pi} = Mean_{patient}/SD_{pi}$, where PI_{upper} = upper boundary of the smoothed prediction interval; *control mean* = the mean predicted by smoothing control mean values; and $Mean_{patient}$ = individual patient's mean value. Values below the mean were calculated in the same way except the 95% prediction interval boundary (PI_{lower}) used the lower boundary since boundaries were not necessarily symmetric.

Attention - Simple Reaction Time Task

Typically developing Controls (TD)

Reaction times were log transformed because, as is often the case, the raw RT distribution was right-skewed and a log transform produced a more balanced distribution. A model with a quadratic term for age was used because the developmental trajectory was curved, not linear (Figure 1). The best model included an effect of age, distinct trajectories for left and right locations and an interaction between location and age. Reaction times were slower to right targets. The left/right difference in younger children was 51 msec and then decreased with age. The majority of developmental change occurred during the first years of development, with little change after age 12 (~300 msec over the range from 6 to 12 years).

Figure 1 about here

Morquio syndrome (MPS-IVa)

RT means for MPS-IVa individuals are displayed in Figure 1a. They were within the confidence limits of healthy development in all cases ($z_{pi} > 2 = 0/12$; black points inside dashed black line, Figure 1). The group mean was shifted towards slower reaction times, with eleven of 12 individuals slower than the control mean (six expected by chance).

In the analysis of group differences, the model with just an $Age^2 \times Condition$ interaction was essentially equivalent to the best model ($\Delta AIC = 0.2$; best model: $Condition \times Age^2 + Group \times Age^2$), which means evidence of a group difference was weak (AIC model selection results are summarised in Appendix 2).

Tyrosinemia III

Individual T3 RT means are displayed in Figure 1b. They were evenly distributed across the control range. Two individuals had response times that were reliably slower than controls ($z_{pi} > 2$) when performance was averaged across target locations (patient 7 – 8.03 years, patient 9 – 17.64 years). The two youngest individuals (patient 1 - 4.40 years, patient 2 - 5.16 years) were on the border ($z_{pi} = -1.92$ and $z_{pi} = -1.90$ respectively).

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5 In group comparisons, the best model included a *Condition X Age² X Group* interaction (AIC
6 model selection results are summarised in Appendix 3). The effect of condition was not strong. There
7 were, however, strong effects of *Age* and *Group*. A model with just main effects of *Age* and *Group*
8 was nearly as good as the best model ($\Delta AIC = 1.97$) and models without these terms had essentially no
9 support ($\Delta AIC=11.12$ and $\Delta AIC=17.19$). The 3-way interaction occurs because T3 individuals are
10 slower than the control mean at the earliest ages, closer to the mean in the middle of the age range and
11 slow again when they are older, but by much less, and then the differences are somewhat different in the
12 different quadrants. These interaction effects are, however, subtle and the small T3 sample makes them
13 potentially unstable.

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16 In sum, orienting and reacting to an abrupt onset was not slowed in MPS-IVa. Most individuals
17 were slower than the mean, but scores were clustered quite closely in the region of the control mean
18 with no individuals outside the control range, so a group difference was not supported. There was some
19 evidence of slowing in T3 and models with a group difference were preferred. RT slowing was
20 concentrated on the youngest and oldest participants. Since the effect is carried by relatively small
21 numbers at the extremes of the age range we should be cautious in our interpretation. Participants
22 between 6 and 15 years old were less clearly different. The lack of differences in MPS-IVa and the
23 relatively modest differences isolated to young and old participants for T3 will influence our
24 interpretation of other reaction time tasks where differences are more marked, although we must keep in
25 mind that speed of processing could be affected in T3.

26 **Visual Search**

27 *Typically developing Controls (TD)*

28 Mean reaction time is plotted in the top panels of Figure 2 and search efficiency in the bottom
29 panels. TD controls increased their overall speed with age (top panels) in both conjunction and feature
30 search. The biggest change occurred during the early years, with changes slowing after about 10 years.
31 Feature search efficiencies were close to zero at all ages (although there was some decline in
32 variability). Accordingly, the best model of feature search included an effect of age but no effect of
33 display size. This means the search for a feature difference happened in parallel across all locations in
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3 the display no matter how many items there were to search, which is the normal pattern (A. M.
4 Treisman & Gelade, 1980). The best model of conjunction search, in contrast, included an interaction
5 between display size and age. Reaction times always increased when there were more distractors, but
6 the time to search each item declined steadily from around 70 to around 32 milliseconds (bottom right
7 panel) over the range between 6 and 19 years. There was also a large drop in variability. This indicates
8 that finding the target in conjunction search requires some degree of item-by-item processing.
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14 Accuracy supported the same pattern. Accuracy in feature search increased across ages (from
15 94% at age 6 to 98% at age 19). There was a difference in accuracy on present vs absent trials (90% vs
16 98% at age 6) that narrowed with age (99% vs 98% at age 19) and models supported an interaction
17 between present/absent and age. There was no effect of display size. The best model of conjunction
18 search accuracy included an interaction between display size and target present/absent and an
19 interaction between age and present/absent. The interaction with age was weak because a model with
20 just a main effect of age was nearly equivalent ($\Delta AIC = 1.23$). The interaction with display sizes occurs
21 because more targets are missed in larger displays. Accuracy increased with age (85% at age 6 vs
22 97% at age 19). These patterns do not modify the interpretation of the reaction time results (where
23 larger displays take longer).
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Figure 2 about here

Morquio Syndrome (MPS-IVa)

42 The biggest difference between individuals with MPS-IVa and controls occurred in the simpler
43 task of feature search. z_{pi} was greater than two in six individuals and between one and two in one other
44 individual. Eleven of 12 individuals were slower than the control mean. Six would be expected by
45 chance. In conjunction search, z_{pi} was greater than two in three individuals and between one and two in
46 four others. Ten of 12 individuals were slower than the control mean.
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52 There were no abnormal increases time to search larger displays (i.e. display size effects were
53 normal). In feature search, additional items took longer in three individuals (Patient 1, $z_{pi} = 2.46$; Patient
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3 8, $z_{pi} = 5.99$; patient 11, $z_{pi} = 11.25$), and, in conjunction search, in two (Patient 8, $z_{pi} = 2.57$; Patient 11,
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5 $z_{pi} = 3.55$).

6
7 Group differences between MPS-IVa individuals and controls were analysed separately for
8
9 feature and conjunction search. The best model of feature search did not include an effect of *Display*
10
11 *Size* and there were no two or three-way interactions. There was a main effect of *Age* (younger
12
13 participants were slower) and a main effect of age (MPS-IVa individuals were 445ms slower than
14
15 controls). Models without terms for *Group* and *Age* were poor.

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17 The lack of interaction between *Group* and *Age* shows that MPS-IVa individuals make progress
18
19 at a normal rate, neither catching up with controls or falling behind, despite the slower overall times.
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21 We should be somewhat cautious about this result, however, because there is a small number of
22
23 individuals at each age.

24
25 In the analysis of accuracy, *Group* was added to the *Age* by *Present/absent* interaction from the
26
27 control model. Instead of the increasing accuracy seen in controls, MPS-IVa individuals initially show
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29 a bias to "present" and later a bias to "absent" with little consistent change to percent correct. This is
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31 not a theoretically important pattern in the present context. Averaging over present/absent conditions,
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33 the best model included an interaction between *Age* and *Group* that resulted from increasing overall
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35 accuracy in controls, but flat or slightly decreasing accuracy in MPS-IVa individuals. MPS-IVa
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37 individuals and controls had equivalent accuracy when averaging across ages (both 94%). Accuracy
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39 does not change the interpretation of reaction times. Accuracy is high in both MPS-IVa individuals and
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41 controls and there was no indication that longer RTs were associated with higher accuracy in the MPS-
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43 IVa group ($R = -0.46$, $p = .13$; a negative R value results when higher accuracy is associated with *lower*
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45 RT).

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47 The top four models of conjunction search were all very similar in their ability to account for
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49 reaction times (*Display size X Age + Group X Age*; *Display size + Group X Age*; *Display size X Age +*
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51 *Group*; *Display Size + Age + Group*; max change in AIC = 0.8). Good models all included terms for
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53 *Display Size*, *Age* and *Group*. Interactions between *Group* and *Age* and between *Display Size* and *Age*
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55 were weak because the simpler model with only main effects was a close equivalent ($\Delta AIC = 0.8$).
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3 It is important to note the lack of interaction between *Display Size* and *Group*. MPS-IVa
4 individuals processed each item as quickly as controls, even when efficiencies were above zero and
5 each item required additional processing time (~42 ms per item in both MPS-IVa and controls). The
6
7 *Group* effect, instead, resulted from a constant amount of slowing at all display sizes (~378 ms for both
8
9 large and small displays). Models without main effects of *Display Size*, *Age* or *Group* were poor.
10
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12 In sum, MPS-IVa individuals were clearly slower in visual search. This difference, however,
13
14 was constant across display sizes. Item-by-item processing was not slowed. The upward shift in
15
16 reaction times without display size effects could have at least two origins. One possibility is that MPS-
17
18 IVa individuals occasionally lose concentration or are distracted. If so, reaction times at the fast end of
19
20 the range should be similar to controls, but there should be more difference in slower reaction times.
21
22 Lapses could be distributed across small and large displays. A second possibility is that a stage that is
23
24 not sensitive to attentional demands, is affected (a non-decision stage, in the terminology of search
25
26 models). This could be time to initiate search or time to select and program a response.
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29 To explore these alternatives, we binned reaction times into quintiles for each participant and
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31 compared quintiles across groups using the vincentizing method (Ratcliff, 1979; see Romani,
32
33 MacDonald, De Felice, & Palermo, 2017 for this kind of analysis in a population of individuals with
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35 PKU). Figure 3 shows reaction times and standardised differences between means for individuals with
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37 MPS-IVa and controls in each quintile. To standardise, we divided the difference between MPS-IVa
38
39 and control means by the standard error of the control mean. Because reaction time distributions have
40
41 an extended tail associated with the longest reaction times, the variance in the final bin is higher than
42
43 the other bins, and interpretation of quintile differences needs to take this increased variance into
44
45 account. We will concentrate on two aspects of the difference curves. We will ask, first, if MPS-IVa
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47 quintile means are slower than controls (difference scores > 0). We will also ask if differences are
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49 increase across quintiles, particularly quintiles 2, 3 and 4, showing increasing differences with longer
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51 reaction times.
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55 Figure 3 about here
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3 With one exception, there were relatively stable differences across the full range of quintiles in
4 MPS-IVa, not increasing differences. In feature search at ages 5-8, conjunction search at ages 8-10.5
5 and both feature and conjunction search at ages 10.5-14 reaction times were always slower, even in the
6 fastest bins ($t > 2.3$; $p < .03$) but differences did not increase. Feature search at ages 8-10.5 was the only
7 condition with increasing differences (conjunction search at ages 5-8 showed no differences, all $t < 1.8$,
8 all $p > 0.08$). The overall pattern does not support distraction/failures of attentional control or the
9 accumulating effects of general slowing. Instead, initiation or response processes are possible loci.

16 Tyrosinemia III (T3)

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18 In feature search, four of eleven T3 individuals had $z_{pi} > 2$ for mean RT. An additional two had
19 z_{pi} between 1 and 2 (Figure 4). In conjunction search, five of eleven individuals had $z_{pi} > 2$ and two had
20 z_{pi} between 1 and 2. Only one individual had a search efficiency z_{pi} greater than two and three had z_{pi}
21 between 1 and 2.
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Figure 4 about here

Group differences were analysed separately for feature and conjunction search. The best model for feature search included an *Age* by *Group* interaction. There were more individuals further from controls at older ages. There was a ~76 ms difference between groups when participants were under 12 years old, with as many T3 individuals below the control mean as above it. Individuals older than 15 years were, on average, ~187 ms slower than controls, and all four T3 individuals were above the mean. There was no effect of *Display Size*, indicating that feature search was efficient for both groups.

The best model for accuracy in feature search included an interaction between *Present/absent*, *Age* and *Group*, adding *Group* to the interaction from the control model. As with MPS-IVa, there was a different pattern of *Present/absent* effects compared to controls. Accuracy was relatively constant, but *Present* trials showed some decrease. Overall, T3 individuals were less accurate than controls (89% vs 93%). There was no evidence of a speed/accuracy trade-off that would modify interpretation of the reaction time results.

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3 In conjunction search, the best model of reaction times included main effects of *Display Size*,
4 *Group* and *Age*, but no interactions to suggest group differences in display size or age effects. The
5 group difference was an average of 71 msec when participants were below 12 years old and 133 ms
6 when participants were above 15 years old.
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10 Models of accuracy in conjunction search included a *Group* by *Display Size* by *Age* by
11 *Present/absent* interaction. The *present/absent* variations are unlikely to be theoretically important.
12 When present/absent conditions were collapsed and individuals put in two age groups to increase N
13 (less than or greater than 12 years old), models required a *Group* by *Display size* by *Age* interaction.
14 Accuracy was lower than controls (80% vs 90%) and the display size effect was larger in younger
15 individuals only (accuracy dropped by 12% when young individuals viewed larger displays, but only by
16 1-3% in older T3 individuals, young controls and old controls).
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24 We examined the source of slower RTs using the quintile method described above. In contrast
25 to MPS-IVa, T3/control differences increased across quintiles (Figure 5). At ages 4.5-6, differences in
26 both search tasks increased in bins 1-3 and then levelled out. At ages 6-8.5 there were no differences
27 from controls. At ages 15-19, differences increased across all bins in both search tasks. In the youngest
28 and oldest T3 individuals, reaction times were different even in the first bin (all $t > 2.3$; $p < .03$), showing
29 that T3 individuals in these groups were always slower, but the differences increased for longer reaction
30 times. Different patterns at different ages should be interpreted with caution because the number of
31 individuals at each age is small.
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46 In sum differences in visual search were sometimes observed more in accuracy and sometimes
47 more in reaction times, but there was a relatively consistent difference. At the level of individuals there
48 was considerable variability. Seven of 11 individuals recorded reaction times that were slower than the
49 control mean in feature search and seven of 11 in conjunction search (not always the same individuals).
50 This was not a marked difference because the value expected by chance is 5.5 (recall that in MPS-IVa
51 nearly all individuals were above the control mean). There was some indication that performance got
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3 worse with age. This was, however, based on small numbers, so we should be cautious about how
4 strongly we interpret the effect. RT quintiles showed increasing differences for longer reaction times.
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6 This was not consistent with increased processing for more difficult displays because 1) the pattern was
7 the same in both feature and conjunction search (difficulty does not increase with display size in feature
8 search) and 2) conjunction search efficiencies (which measure increasing difficulty) were normal. It is
9 possible that occasional long reaction times were based on distraction, but this would not account for
10 the differences in the first quintiles. There may also be slowing which affects all quintiles, as in MPS-
11 IVa, during initiation or response stages. We will return to the issue of distraction when we discuss the
12 fixation task.
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21 **Language**

22 *Typically developing Controls (TD)*

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24 Control participants showed improvement with age in both the BPVS ($\Delta AIC = 163$) and the
25 BNT ($\Delta AIC = 58$; Figure 6).
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32 Figure 6 about here
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35 *Morquio Syndrome (MPS-IVa)*

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37 Patient 12 did not complete the Boston Naming Test (*BNT*) because of time constraints. *BPVS*
38 and *BNT* scores are shown in Figure 6a. On the Boston Naming Test, one individual scored below the
39 control mean (patient 6; $z_{pi} = -3.17$) and one scored above (patient 7; $z_{pi} = 2.74$). Three other individuals
40 had z_{pi} between -1 and -2. The best model for the Boston Naming Test included only a term for changes
41 with age. There was no evidence that MPS-IVa individuals performed worse than controls.
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48 No *BPVS* scores were further than two standard deviations below the mean, but 7/12
49 individuals were between one and two standard deviations below (Figure 7). The best model for *BPVS*
50 scores included an interaction between *Group* and *Age*, but evidence for the interaction was weak
51 because the model without the interaction was nearly equivalent ($\Delta AIC = 0.7$).
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3 In sum, MPS-IVa individuals showed no difference from controls in productive vocabulary and
4 only minor differences in receptive vocabulary with no individuals or very few outside the control
5 range.
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8 *Tyrosinemia III (T3)*

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10 Just over half of the T3 individuals were more than two standard deviations below the mean on
11 the *BNT* (6/10 individuals). The best model for *BNT* results included an interaction between *Age* and
12 *Group*. The difference between T3 individuals and controls widened with age (Figure 6b). The
13 difference at the earliest ages was 18, but widened to 56 in the oldest individuals.
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18 On the *BPVS*, the majority of T3 individuals were more than two standard deviations below the
19 mean (8/11 individuals). The best model included an interaction between *Age* and *Group*. Once again,
20 the difference between T3 individuals and TD controls got larger with age (Figure 8). At the earliest
21 ages (6 years) the estimated difference was 32 points. By 19, the estimated difference had grown to 63
22 points. Models without terms for either *Age* or *Group* were poor.
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28 Unlike MPS-IVa, where the differences from controls were small, T3 individuals show clear
29 problems with language tasks that become more marked with age.
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33 **Oculomotor Tasks**

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35 Oculomotor tests included a fixation task and a saccade task. Morquio patients 5 and 7 did not
36 want to attempt the saccade task and patients 2, 3, 4 and 11 did not complete all saccade trials due to
37 fatigue. T3 patient 2 was unable to complete the oculomotor tasks due to postural difficulties which
38 prevented eye tracking.
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43 **Fixation task – Dwell time**

44 *Typically Developing Controls*

45
46 *Dwell time* is the total time spent fixating the target during a trial (summing initial fixation and
47 re-fixation times). Dwell time in controls was described by a quadratic model with an interaction
48 between *Condition* and Age^2 (Figure 7). Systematic modelling revealed some advantage for top
49 targets, but this was subtle.
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Figure 7 about here

Morquio Syndrome (MPS-IVa)

The majority of MPS-IVs individuals exhibited fixation dwell time deficits (Figure 7a; $z_{pi} < -2$ in 8/11 individuals). The best model of MPS-IVa and control data included all 2-way interactions. The *Group X Condition* interaction reflected differences between quadrants that were larger for MPS-IVa individuals than controls (control maximum difference, top vs bottom = 160 msec; MPS-IVa maximum difference, top vs bottom, 906 msec). The *Group X Age²* interaction reflected larger differences between groups at younger ages. The model without this interaction was nearly equivalent, however, so the difference was weak ($\Delta AIC=2.1$). The strongest difference was that MPS-IVa individuals fixated the target for considerably less time than controls (difference = -1083 msec), and a model without the *Group* term was poor (*Condition X Age²* model, $\Delta AIC = 55$).

Tyrosinemia Type III (T3)

Results are presented in Figure 7b. As a group, T3 dwell times were shifted below the control mean (Average $z_{pi} < 0$ in 8/10 individuals), with four individuals who were different enough to be completely outside the control range. The best model of T3 and control data included interactions for *Condition X Age²* and *Condition X Group*. The *Condition X Group* interaction reflected differences between quadrants that were larger in T3 individuals (maximum difference of 158 msec in controls compared to 528 msec in T3). There was a group difference (model without Group, $\Delta AIC = 17$), but it was smaller and carried by fewer individuals than in MPS-IV.

Fixation Task – Intrusive Saccades*Typically Developing Controls*

The number of intrusive saccades, where fixation moved away from the target during the period when participants were supposed maintain fixation, was defined by a quadratic function (Figure 7) where the majority of age-related change occurred before 10 years. A model which included a *Condition X Age²* interaction was clearly better than a model that did not ($\Delta AIC = 8$). There were some minor differences due to location (fewer intrusive saccades for top targets) but these were subtle.

Morquio syndrome (MPS-IVa)

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3 Seven MPS-IVa individuals made more intrusive saccades than controls (7/11 $z_{pi} > 2$; Figure
4 7a). These seven also had shorter dwell times. Dwell time would be expected to be shorter when there
5 are frequent intrusive saccades. One individual, however, was within the control range for intrusive
6 saccades but not dwell time (patient 7). They held their first fixation on the target for a shorter time but
7 did not go back and forth between the target and other locations. Examples of saccade and fixation
8 deficits in two individuals are shown in Figure 8.
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21 The best model of group differences included a main effect of *Group* and an interaction
22 between *Age*² and *Condition*, showing that intrusive saccade suppression was poorer in MPS-IVa
23 compared to controls.
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25 26 *Tyrosinemia III (T3)*

27
28 Unlike MPS-IVa, intrusive saccade frequencies were normal in the majority of T3
29 individuals (Figure 7b; 8/10 $z_{pi} < 2$). Two older individuals (patient 9 and 11) had more substantial
30 problems across target locations. Importantly, patient 9 also exhibited fixation time deficits, and it is
31 clear from the eye movement traces that fixation on the target was disrupted by intrusive saccades
32 towards the screen centre. Group differences were best explained a model with *Group X Age*² and
33 *Condition X Age*² interactions, but a model with without an effect of *Group* was essentially equivalent
34 ($\Delta AIC = .05$).
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44 **Pro-saccade Task – Saccade Onset time**

45 *Typically Developing Controls*

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47 Figure 9 plots saccade onset times for TD controls. Saccade onset time decreased with age and
48 the majority of change occurred between 5 and 12 years. The data were log transformed because
49 residuals increased at higher values. There was a clear preference for a model that included an *Age X*
50 *Condition* interaction. A model with separate trajectories for top and bottom targets, and a shared
51 trajectory for horizontal targets was best. The location that took longest to react to at 6 years old was the
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3 bottom target (max bottom, 307 ms vs min right, 247 ms). At older ages the differences narrow and the
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5 order changes (max top, 186 ms vs min right, 161 ms at 19 years).
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Figure 9 about here

MPS-IVa (Morquio syndrome)

Individual MPS-IVa saccade onset values are shown in Figure 9a. All MPS-IVa individuals were within the control range. The best model included an interaction between *Group* and *Condition* and *Age* and *Condition*. Group differences varied some by target location, but there was not an interpretable pattern and there was no evidence of a main effect of group independent of the interaction with condition (The model with just an *Age X Condition* interaction was better than the model that included an *Age X Condition* interaction and a main effect of *Group*, $\Delta AIC = 1.39$; means collapsing across location differed by less than 1 msec).

Tyrosinemia type III

Individual T3 saccade onset values are shown in Figure 9bf. Averaged across target locations, only one individual (patient 9, 17.98 years) had a $z_{pi} > 2$. This individual also had fixation time and intrusive saccade deficits. Models of saccade onset did not support a group difference.

In sum, neither metabolic disease group was systematically slower to initiate saccades.

Pro-saccade Task – Saccade Peak Velocity

There was no evidence of differences in saccade velocity when either disease group was compared to controls. The preferred model for MPS-IVa did not include a term for *Group*. The T3 model without a *Group* term was essentially equivalent to the best model ($\Delta AIC=0.6$).

Discussion

We examined cognitive functioning in two rare inherited metabolic diseases – Morquio syndrome (MPS-IVa) and tyrosinemia type III. We compared individuals with metabolic disease to controls using formal tools for model selection and a developmental trajectory approach. This provided

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3 a richer way of evaluating developmental differences than traditional age-matched comparisons. We
4 were able to separate different types of developmental effects, including changes to the *rate* of
5 development and constant decrements in performance in the presence of a normal rate of development.
6 We included both analysis of group performance and individual comparisons (based on prediction
7 intervals). These contributed different, but complementary information.
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13 In both diseases we found cognitive effects, but with different functional profiles, showing that
14 metabolic disease creates specific cognitive effects, and does not just produce homogenous and general
15 decrements in performance. Sustained attention was affected in MPS-IVa and language, especially, but
16 also sustained attention in T3. These are potential candidates for sensitive markers of disease
17 progression and they document selective functional impacts that can be considered alongside
18 descriptions of biological changes. A summary of effects across cognitive domains is shown in Table 1.
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25 *MPS-IVa (Morquio Syndrome)*

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27 Few studies have investigated cognitive performance in MPS-IVa (Morquio syndrome),
28 primarily because clinical observations report normal intellectual function (Dvorak-Ewell et al., 2010;
29 Wraith, 2006). A recent study, however, reported mild cognitive changes (Davison et al., 2013) and
30 highlighted difficulties with attention. We did more detailed cognitive testing and we also found
31 attention deficits in several tasks. Fixation dwell time was lower and disrupted by intrusive saccades.
32 MPS-IVa individuals had difficulty sustaining attention after the natural engagement created by an
33 abrupt visual onset had ended. Visual search times were slower, but without a decrease in search
34 efficiency. Item-by-item processing was normal. Analysis of the reaction time distributions showed
35 that both fast and slow search times were delayed and differences did not increase for slower reaction
36 times. This was *not* consistent with occasional lapses of attention, which should introduce larger
37 differences for slower reaction times. There was no evidence of general slowing since simple reaction
38 time, saccade onset times and saccade velocities normal or only weakly affected and differences did not
39 increase with difficulty (slower RTs were not more delayed and search efficiencies were normal).
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Instead, search results point to delays in a stage that is unrelated to attentional demands, like task preparation or response decision, which would slow both fast and slow responses. We did not find a

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2
3 natural connection that links results from the fixation task and visual search. Each task suggested a
4 different deficit. If there was a connection between them this is not currently clear.

5
6 An offset in search times, with slower times overall, but not slower item-by-item processing
7 (i.e. unchanged effects of display size) has been reported under several conditions in the literature, most
8 importantly, under a working memory load and in aging. When a non-spatial working memory task
9 must be completed at the same time as visual search, search slows but search efficiency is unchanged
10 (Oh & Kim, 2004; Woodman, Vogel, & Luck, 2001). Older adults also show slower search times,
11 without increased display-size effects (Gorman & Fisher, 1998; Monge et al., 2017; see also Ratcliff,
12 Thapar, & McKoon, 2006 for a similar increment in a discrimination task that is attributed to “non-
13 decision” aspects of the task). Reduced capacity could be a factor in common between aging and dual
14 tasking and may also explain our results, but note that this cannot be the same as general slowing since
15 in MPS-IVa both simple RT and saccade onset times were either unaffected (saccade onset time) or
16 only weakly affected (simple RT).
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28 The fixation task may index the difficulties with sustained attention reported by parents in the
29 Davison et al. (2013) study. Difficulties concentrating could be the everyday consequence of the same
30 problem that reduces fixation times during formal testing. Indeed, maintaining fixation involves
31 mechanisms that are not isolated within the system for eye-movement control. The areas that are
32 responsible for maintaining fixation (Krauzlis, Goffart, & Hafed, 2017), including areas in dorso-lateral
33 prefrontal cortex, the frontal eye fields and the superior colliculus, are areas that have connections to
34 other modalities: auditory or proprioceptive, in the case of the frontal eye fields (Medendorp,
35 Buchholz, Van Der Werf, & Leoné, 2011); or movement control, in the case of the superior colliculus
36 (Krauzlis et al., 2017). The frontal eye fields, for example, are thought to “encode ‘supramodal’
37 representations to guide attention and behaviour” (Medendorp et al., 2011). Problems in these areas
38 could plausibly be the source of general attentional issues.
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50 In sum, our results highlight difficulties in MPS-IVa with sustained attention and with task
51 preparation or response decisions. They extend the preliminary results reported by Davison et al.
52 (2012) and they show that the differences in attentional tasks occur without commensurate changes in
53 other cognitive tasks (e.g. language tasks; item-by-item processing in selective attention) or general
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3 slowing (as reflected in normal or near normal simple reaction time, saccade onset and saccade
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5 velocity).

6 7 *Tyrosinemia III (T3)*

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9 In Tyrosinemia III, there were clear deficits in both language production (*BNT*) and
10
11 comprehension (*BPVS*) and differences from controls appeared to widen with age.

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13 There were also differences in average search times, simple RT and dwell time. Item-by-item
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15 processing in visual search was not affected (the same pattern as MPS-IVa), but the differences between
16
17 T3 and controls were more marked for longer reaction times, consistent with occasional attentional
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19 failures (different from MPS-IVa). Dwell times in the fixation task also pointed to problems sustaining
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21 attention. There was some evidence of slowing in simple RT. Slowing, like lapses in attention, predicts
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23 differences that increase with difficulty, consistent with the conjunction search results. Slowing,
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25 however, does not provide a good account other aspects of the pattern because: 1) Display size effects
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27 in conjunction search were normal and slowing predicts larger differences for more difficult conditions;
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29 2) Simple feature search produced the same pattern as conjunction search--increasing differences with
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31 slower RTs--but larger displays are not more difficult in feature search, showing that slowing occurs
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33 even when there is no change in difficulty; 3) There was no evidence of slowing in saccade onsets or
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35 saccade velocity. Search RT differences were larger for slower RTs, but even the fastest T3 search RTs
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37 were slower than controls. This means that lapses in attention do not explain the whole T3 pattern and,
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39 like MPS-IVa, there must be problems that are unrelated to attentional demands.

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41 To our knowledge, this study represents the most detailed cognitive assessment of T3 to date
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43 and highlights, especially, language impairments, but also problems with sustained attentional and age-
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45 related decline. Our results provide formal tests to confirm and extend the case-based findings of
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47 Ellaway et al. (2001), who described mild to moderate intellectual impairments in a sample of 12
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49 individuals, but without specific information about cognitive testing.

50
51 The prevalence of language deficits is a frequently-reported cognitive feature of T1 individuals
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53 treated with NTBC (Bendadi et al., 2014; Thimm et al., 2011). Since NTBC treatment blocks the
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55 biochemical pathway at the same place it is blocked in T3, treated T1 resembles T3, except that T1
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57 individuals are subject to both high levels of tyrosine and potential collateral effects of NTBC.
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3 Our results suggest that the cognitive impairments in T1 are related to the high levels of
4 tyrosine rather than NTBC. Several lines of evidence converge on this. Our T3 individuals have raised
5 tyrosine but no NTBC and they have similar impairments to treated T1 individuals. Learning
6
7 impairments are present in the mouse model of T1 after NTBC treatment, but not in healthy mice who
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9 are given NTBC, suggesting that raised tyrosine is the source of impairment, not NTBC (Hillgartner et
10
11 al., 2016). Finally, Ellaway et al. (2001) reported that T3 individuals who were put on a low tyrosine
12
13 diet later had more severe symptoms than individuals who began a diet earlier and Ellaway et al.
14
15 speculated that elevated tyrosine levels in cerebrospinal fluid (CSF) were particularly damaging during
16
17 infancy. We did not analyze biochemical data, but some of the variance in the cognitive performance in
18
19 our sample could result from individual differences in tyrosine levels that, in turn, could be based on
20
21 variations in early exposure or dietary compliance. Relating tyrosine concentrations at different ages to
22
23 cognitive performance will be an important step toward understanding how and when tyrosine affects
24
25 the brain and when dietary control is critical for effective treatment.
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29 The behavioural consequences for T1 mice treated with NTBC are worth noting in relationship
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31 to the language deficits we found. Hillgartner et al (2016) found that NTBC treated T1 mice were
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33 slower to learn in a maze task. Both the BNT and the BPVS are tests of vocabulary. That is, they test
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35 the facility with which words are processed *or stored* in the mental dictionary. Both tests would be
36
37 sensitive to problems with word learning. It could be word *learning*, rather than a deficit affecting
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39 phonological or lexical representations directly, that is the source of differences in our T3 individuals.

40 *The cognitive neuropsychology of metabolic disease*

41
42 Our results show that neurodegeneration from metabolic disease is not a uniform process.
43
44 We did not find homogeneous declines across diseases and tasks. Patterns from were different. There
45
46 was a diversity of preserved and impaired capacities across language, sustained attention, selective
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48 attention and processing speed even if the precise underlying mechanisms are difficult to pinpoint at
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50 this stage. Since the different metabolic diseases affect different chemical systems in the brain, this
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52 shows that neuro-cognitive systems are not just differentiated by anatomical location. Brain networks
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54 critical for different cognitive functions are differentially sensitive to specific cellular support systems.
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56 We can begin to ask “why?” Are there systems, for example, that are particularly sensitive to neural
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3 transmission speed, network synchronization, specific neurotransmitters, growth or membrane
4 changes—all properties that would be directly influenced by the biochemical environment? What is
5 the *functional* aspect of the system that makes these characteristics critical? This is a relatively
6 unexplored dimension, within neuropsychology, that is orthogonal to the understanding of anatomical
7 loci and networks. These questions will be critical, however, to understanding the brain as an integrated
8 biochemical and anatomical system and they will be critical to our understanding of disease.

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14 For MPS-IVa, what we can say about the relationship between metabolic processes and
15 cognition is limited because it has typically been described as a condition that doesn't have cognitive
16 impacts. As a result, there has been little effort to explain how a deficiency in *N*-acetylgalactosamine-6-
17 sulfatase (GALNS) might affect the brain. Davison et al. (2013) were probably the first to offer some
18 possibilities. GALNS breaks down karatan sulfate and chondroitin-6-sufate, and these substances help
19 coordinate neuroaxonal connection formation (Miller, Sheppard, & Pearlman, 1997). In addition, MPS
20 IVa may affect calcium signalling, and connections between calcium signalling, mitochondria and
21 neurodegeneration have been made for Huntington's disease, amyotrophic lateral sclerosis, Alzheimer's
22 disease and Parkinson's disease (Marambaud, Dreses-Werringloer, & Vingtdeux, 2009). Finally,
23 calcium signalling plays an important role in long term potentiation and excitotoxicity, two additional
24 routes to cognitive effects (Marambaud et al., 2009).

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36 Tyrosinemia type III, allows more specific hypotheses. As we have noted, T3 involves a
37 defect in the enzyme which is needed to break down tyrosine, and tyrosine is a precursor of both
38 dopamine and norepinephrine. This creates several avenues for cognitive effects, as outlined by
39 Hillgartner et al. (2016) in their discussion of NTBC-treated T1: 1) increased tyrosine; 2) increased
40 dopamine (produced by conversion from tyrosine); 3) decreased large amino acids (because they are
41 outcompeted by tyrosine, including tryptophan, the precursor of serotonin); or 4) decreased serotonin
42 (due to lack of precursor). Hillgartner et al., however, go on to hypothesize that cognitive problems in
43 NTBC-treated T1 are unrelated to any of these primary effects, and are caused, instead, by two by-
44 products of defective tyrosine break-down: one that is neurotoxic (succinylacetone) and the other that
45 is both neurotoxic and causes demyelination (δ -ALA). This is possible if, as Hillgartner et al. speculate,
46 NTBC is poorly transported into the brain, and tyrosine catabolism in the brain proceeds past the point
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3 where NTBC treatment stops it in the rest of the body. The problem with this hypothesis is that it
4 cannot explain cognitive effects in T3. The enzyme that is defective in T3 acts at the same point that
5 NTBC acts, but it will be defective in all cells, including those in the brain. The toxic by-products that
6 Hillgartner et al., identify are not produced in T3, but our results show that there is still cognitive
7 impairment, pointing to some combination of the primary biochemical effects as the cause.
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12 *Cognitive neuropsychology of development*

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14 The study of cognitive development in populations with inherited metabolic disease
15 presents both challenges and opportunities (see also, for example, Pitchford & Funnell, 1999).
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17 Development involves changes over time and also potential dependencies among changing capacities.
18 Theories of development must specify the time course of intrinsic or environmentally conditioned
19 change, the environmental inputs that are required for development, and potential dependencies among
20 capacities. The pattern of dependencies that support successful development is not guaranteed to
21 persist when the system is mature, which means that development cannot be transparently inferred from
22 either the mature system or insults to that system.
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30 The complexity of the relationship between adult and developmental models can be illustrated, in
31 terms that will be familiar to readers of *Cognitive Neuropsychology*, in the domain of reading. It is
32 relatively clear, from cognitive neuropsychological results, that sub-lexical and lexical mechanisms for
33 reading are largely independent components in the mature system and all major reading models include
34 them (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Harm & Seidenberg, 1999; Zorzi, 2010).
35
36 The relative independence of these systems in adulthood, however, does not mean that they are
37 independent during learning. This is apparent from developmental dyslexia (e.g. Hulme & Snowling,
38 2016) or more directly, in the context of the current discussion, from acquired dyslexia after a stroke in
39 childhood (Pitchford & Funnell, 1999). As they have in other areas of neuropsychology, the
40 consequences of brain damage can reveal properties of components and dependencies in a
41 *developmental* (rather than a static) model that are not available in other ways. Although there are
42 many studies of developmental cognitive difficulties, the approach that involves characterising
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3 components and dependencies in a detailed *developmental* cognitive model, of the sort that readers of
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5 *Cognitive Neuropsychology* would find familiar, is relatively underdeveloped.³

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7 Our results are too preliminary to show this promise except in outline, but they do show that
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9 developmental effects from metabolic disease can be selective enough to allow tests of functional
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11 models and they illustrate both some methodological issues and some approaches that offer solutions.

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13 One of the basic problems is that development is a moving target. The statistical models of
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15 developmental trajectories that we have introduced here provide some solutions. They allowed us to
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17 compare individuals in disease groups and controls across a range of ages when performance is
18
19 changing and to separate offsets, which create differences across all ages, from changes to
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21 developmental rates. Age did not substantially modify the group differences in visual search or
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23 fixation tasks for MPS-IVa. There were differences at all ages. Age, instead, did modify T3 language
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25 results, where there appeared to be age-related decline.

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27 Capturing developmental trajectories becomes an even more powerful tool when longitudinal data
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29 are available. Trajectories from individuals with disease can be compared to control trajectories.
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31 Variance in *rates* of development will show whether there is, for example, consistent decline, or
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33 heterogeneity in the impact of disease over time. If individuals need to be tracked clinically,
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35 longitudinal trajectories could identify individuals who are not following the normal course of
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37 development before their performance is different from controls at any single point in time, providing a
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39 more sensitive test of disease progression.

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41 The issue of sensitivity and the contrast between what is apparent in individual data and group data
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43 is already clear with our samples. Effects in some individuals that do not occur in all individuals in the
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45 group are common. Data from a group, however, can also show that there are deficits even when the
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47 individual data do not. Conjunction search results for MPS-IVa were a case in point. Only 3
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49 individuals were outside the control range, but the population, as a whole, was clearly shifted toward
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51 slower RTs, with only two individuals faster than the control mean. There is a very low probability that

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54 ³This is not to deny that lexical and sub-lexical mechanisms can display dissociations also during
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56 development (see summary in Castles, Bates, & Coltheart, 2006), but these dissociations do not exclude the
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58 possibility that there are also learning *dependencies* between components that could be revealed by developmental
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60 studies in a way that is not possible in adults (as Castles, Bates & Coltheart, 2006, note, p. 881, and as the methods
of Pitchford & Funnel, 1999, illustrate).

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3 so many scores would be slower the control mean in an unimpaired sample. This is clinically important
4 because it highlights the limits of individual samples for some questions (i.e. is there impairment from
5 disease in this group or not?) and also reinforces the point that techniques like longitudinal sampling
6 may be needed to detect decline at the earliest possible moment in individuals.
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10 The statistical approach we have adopted is a powerful method to deal with developmental data and
11 with relatively small samples. There are, however, limits that small samples, which are inevitable in
12 rare diseases, impose. We cannot, for example, say very much about whether a group trajectory derived
13 from cross-sectional data is a good representation of how diseases progress in *individuals*, and we have
14 avoided fitting a trajectory to the disease groups. In a small sample, especially with relatively high
15 variability, the precise shape, inclination or location of the trajectory can be highly unstable and shows,
16 again, the need for longitudinal data. When the changes over time are clearer, as in the T3 language
17 data, the statistical models give stronger support to the interaction between group and age. Even when
18 this is the case, however, the precise location or shape of the trajectory may be relatively uncertain.
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28 **Conclusion**

29
30 Our study introduces new data and methods that illustrate the promise of cognitive assessment for
31 inherited metabolic diseases. Two cohorts showed that specific measures were sensitive in each disease
32 (e.g. sustained attention in MPS-IVa or language in T3) and could be developed further into new tools
33 to help track disease progression or quantify treatment benefits. In addition, we have shown how
34 cognitive assessment can help to reveal the biochemical basis of cognitive effects. Finally, our results
35 make several extensions possible. Cognitive performance can be related to changes in structure,
36 activity or biochemistry as measured by MRI, fMRI, MRS or EEG to triangulate the biological basis of
37 cognitive changes. Our analysis of different aspects of performance show, however, that a detailed
38 *functional* description of cognitive processes will remain a central component of this project. Extending
39 the methods described here to longitudinal data is a promising next step for understanding the cognitive
40 impacts of inherited metabolic diseases.
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Table 1: Summary of cognitive deficits across cognitive domains.

Task	MPS-IVa				Tyrosinemia III			
	Number of patients with scores worse than control mean	Number of patients with $z_{pi} > 1$	Number of patients with $z_{pi} > 2$	Evidence of control/patient difference?	Number of patients with scores worse than control mean	Number of patients with $z_{pi} > 1$	Number of patients with $z_{pi} > 2$	Evidence of control/patient difference?
Simple reaction time	11/12	3/12	0/12	weak	7/11	4/11	3/11	yes
Visual search								
Feature search								
Overall search time	11/12	7/12	6/12	yes	7/11	6/11	4/11	older patients
Effect of display size increasing differences across quintiles?	7/12	5/12	3/12	no	1/11	1/11	0/11	no
Increasing differences across quintiles?				no				yes
Conjunction search								
Overall search time	10/12	7/12	3/12	yes	7/11	7/11	5/11	yes
Effect of display size increasing differences across quintiles?	6/12	2/12	2/12	no	4/11	3/11	1/11	no
Increasing differences across quintiles?				no				yes
Language								
Boston Naming Test	7/11	4/11	1/11	no	9/10	8/10	6/10	yes
BPVS	9/11	7/11	0/11	weak	11/11	10/11	7/11	yes
Oculomotor tasks								
Fixation task								
Dwell time	11/11	10/11	8/11	yes	9/10	6/10	2/10	yes
Intrusive saccades	9/11	7/11	5/11	yes	3/11	2/11	1/11	no
Prosaccade task								
Onset time	5/9	1/9	0/9	no	5/9	2/9	1/9	no
Saccade velocity	6/9	1/9	0/9	no	1/9	0/9	0/9	no

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A) MPS-IVa

B) Tyrosinemia III

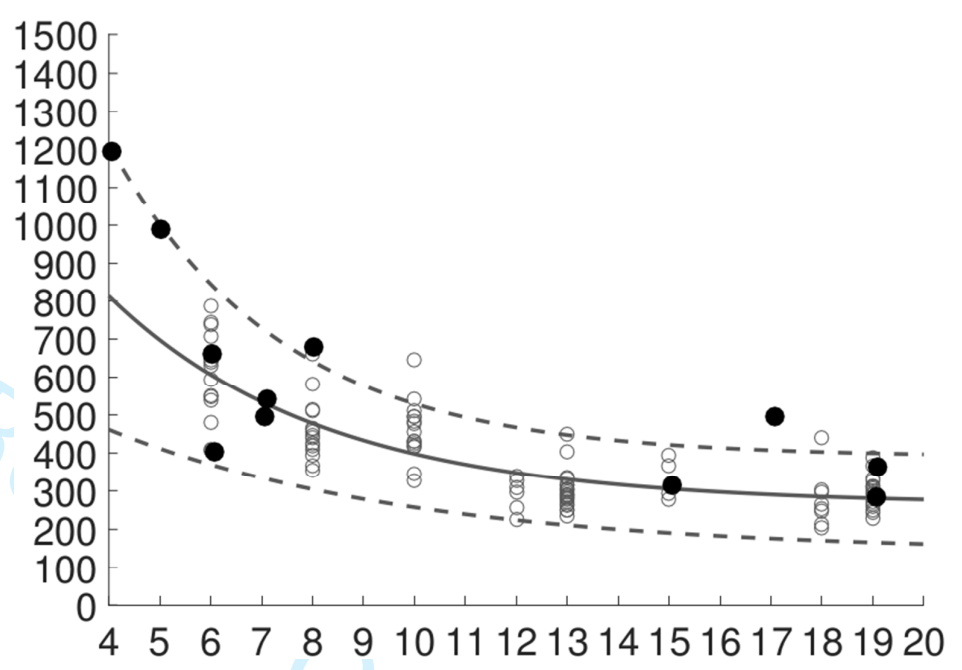
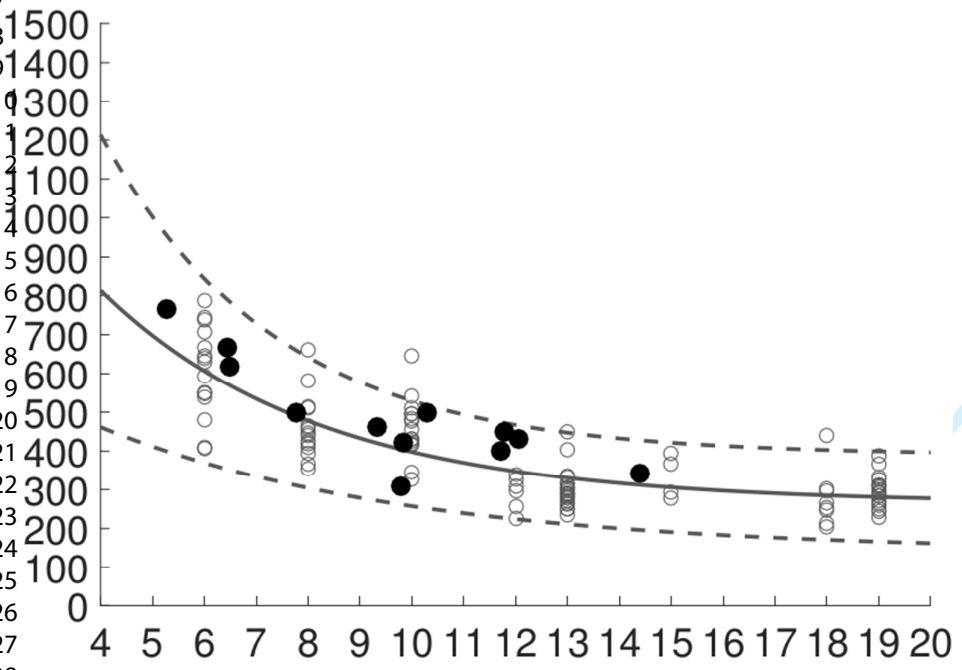


Figure 1. Mean simple reaction time for (A) MPS-IVa and (B) Tyrosinemia III individuals (filled circles) and typically developing controls (open circles). The developmental trajectory for controls is plotted as a solid line with 95% prediction intervals (dashed lines). Reaction times are collapsed across target locations.

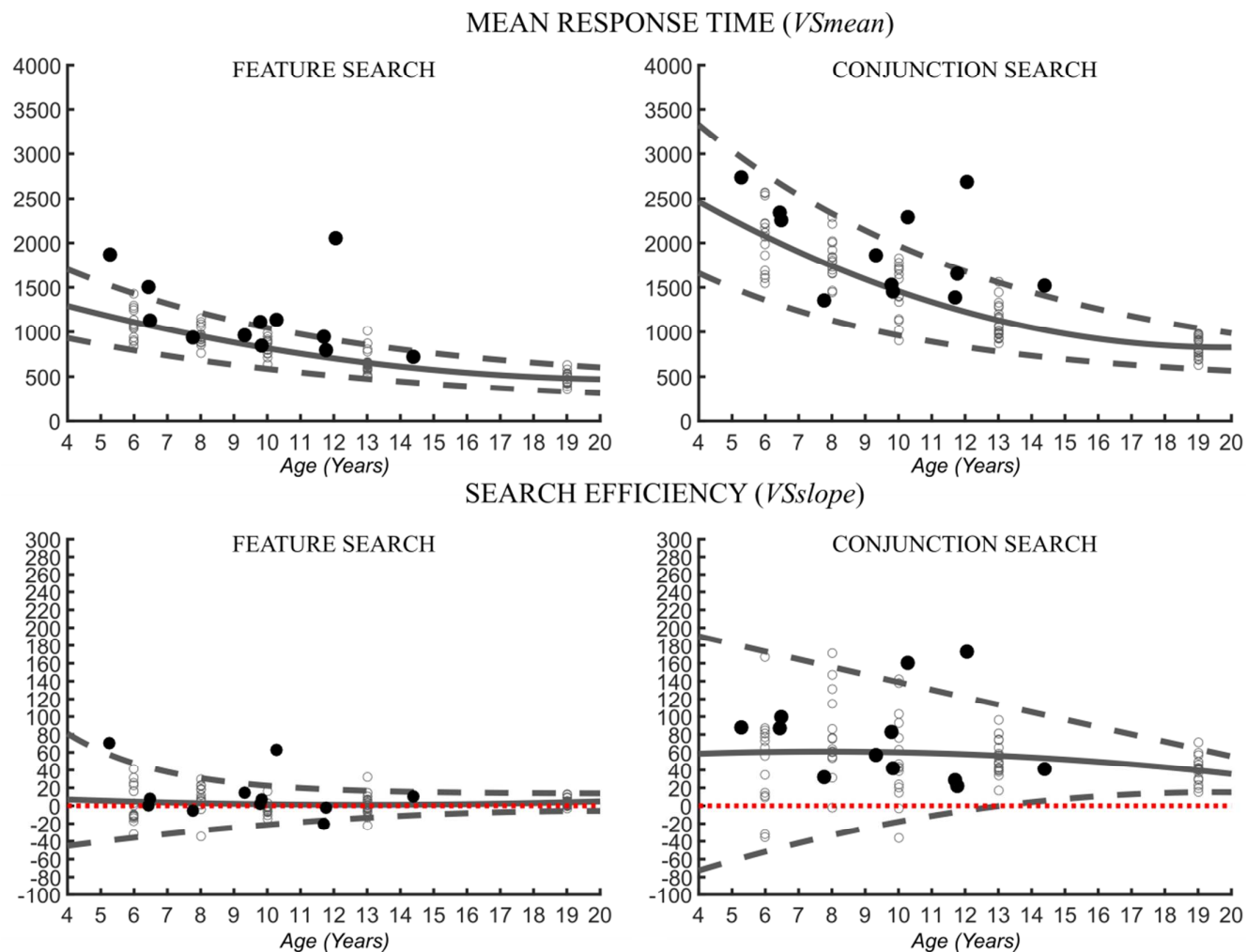


Figure 2. Overall mean RT and search efficiencies (display size slopes) in a visual search task for MPS-IVa individuals (filled circles) and controls (open circles). Feature search results are in the left panels and conjunction search on the right. The developmental trajectory for controls are plotted as a solid line with 95% prediction intervals (dashed lines). The red dotted line in the efficiency plots represents efficient search (no increase in reaction time for larger displays).

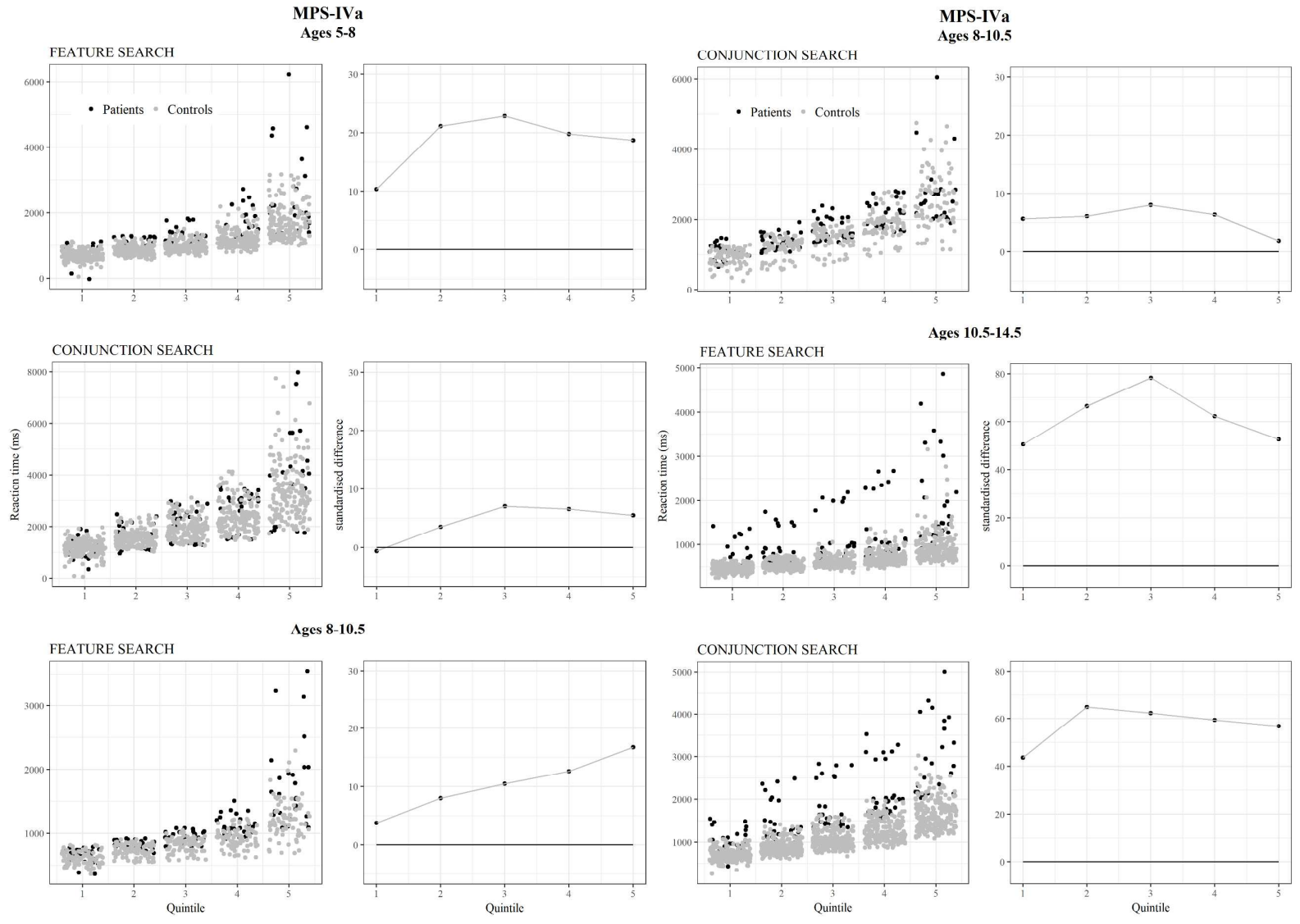


Figure 3. MPS-IVa and Control reaction times from feature and conjunction search. Reaction times are displayed in quintile bins along with the difference between quintile means for patients and controls (control value = 0). Differences between means were standardised by the standard error from the control bin. Note change in scale for final two difference plots.

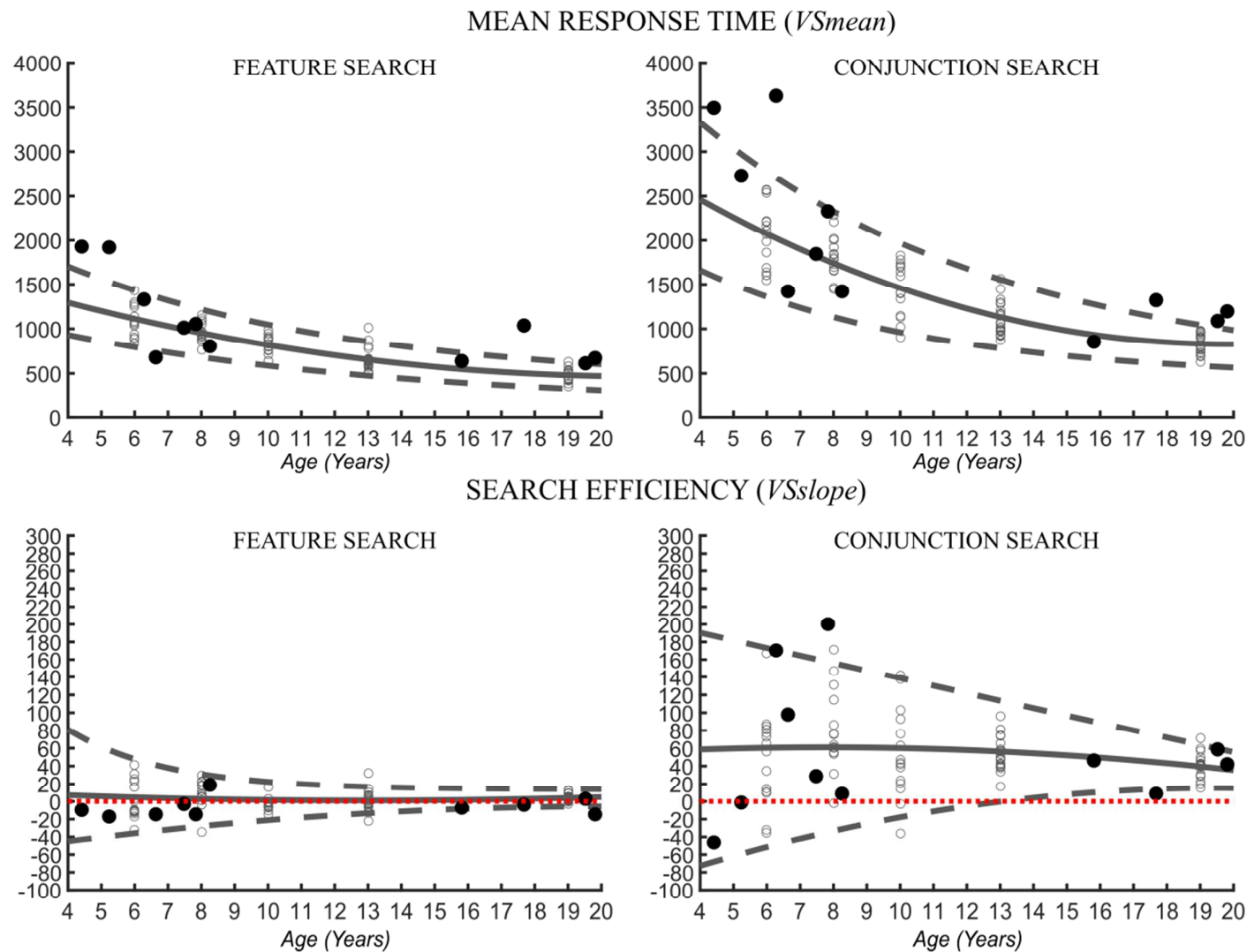


Figure 4. Overall mean RT and search efficiencies (display size slopes) in a visual search task for T3 individuals (filled circles) and controls (open circles). Feature search results are in the left panels and conjunction search on the right. The developmental trajectory for controls are plotted as a solid line with 95% prediction intervals (dashed lines). The red dotted line in the efficiency plots represents efficient search (no increase in reaction time for larger displays).

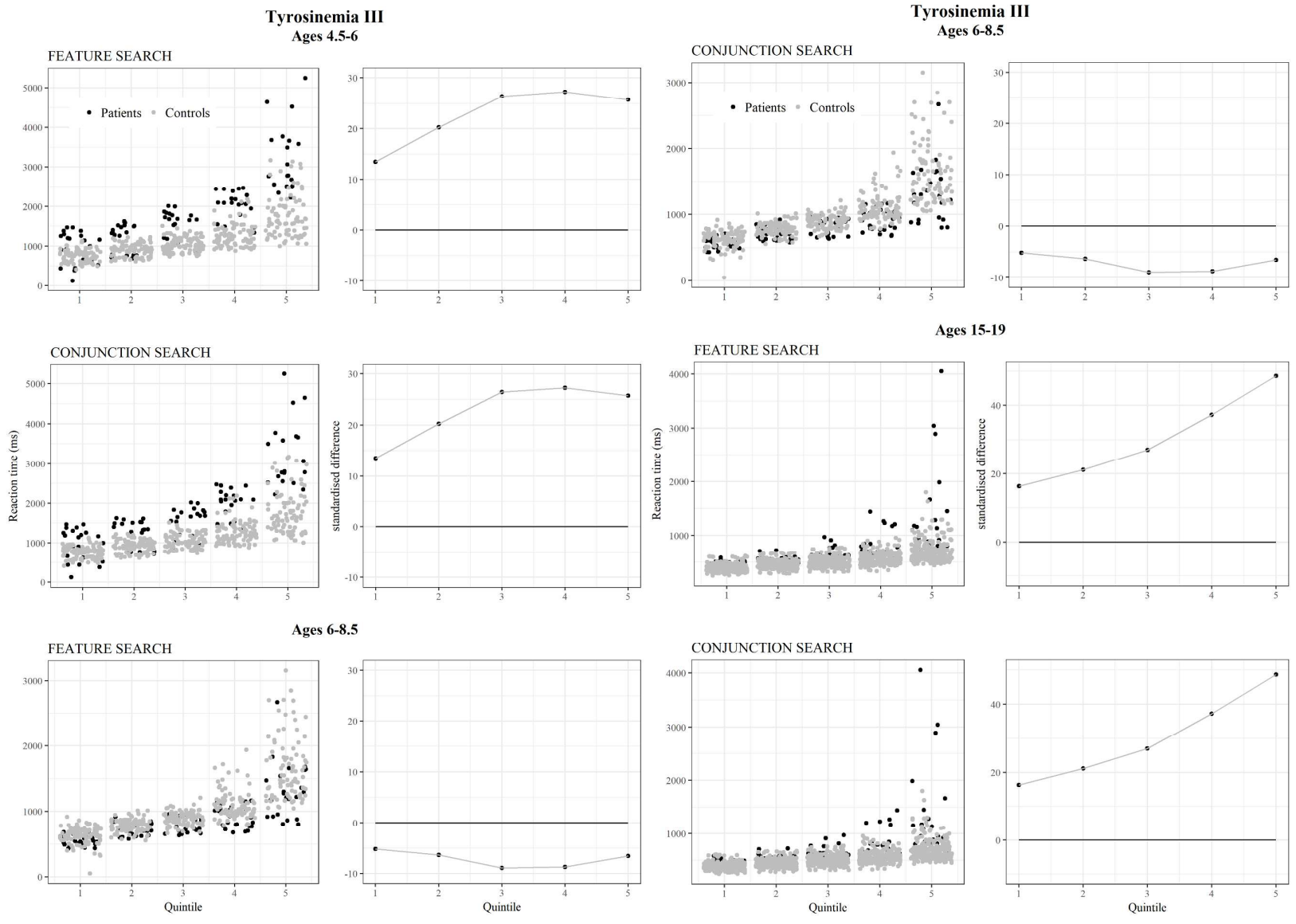
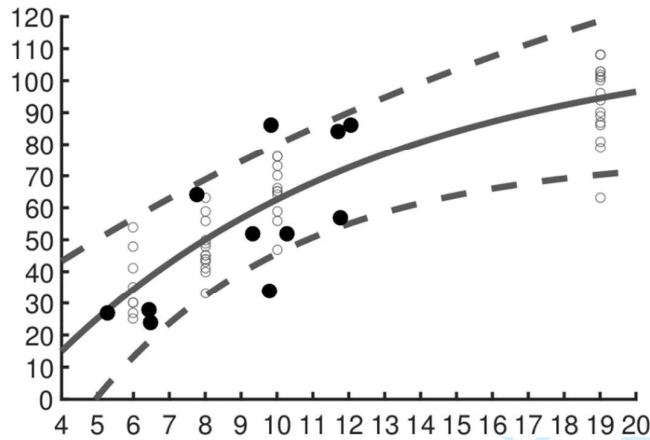


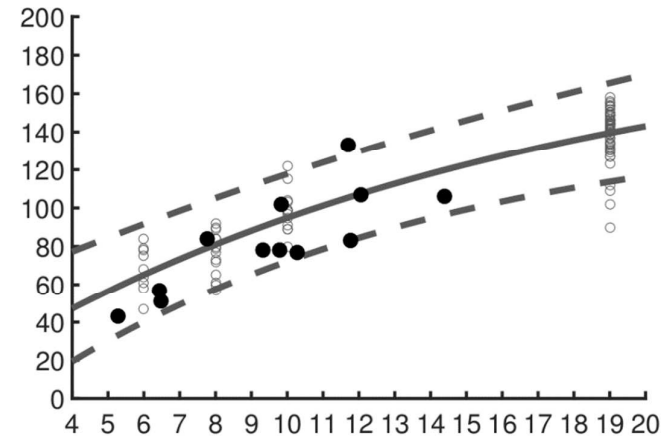
Figure 5. Tyrosinemia III and Control reaction times from feature and conjunction search. Reaction times are displayed in quintile bins along with the difference between quintile means for patients and controls (control value = 0). Differences between means were standardised by the standard error from the control bin. Note change in scale for final two difference plots.

A) MPS-IVa

BNT

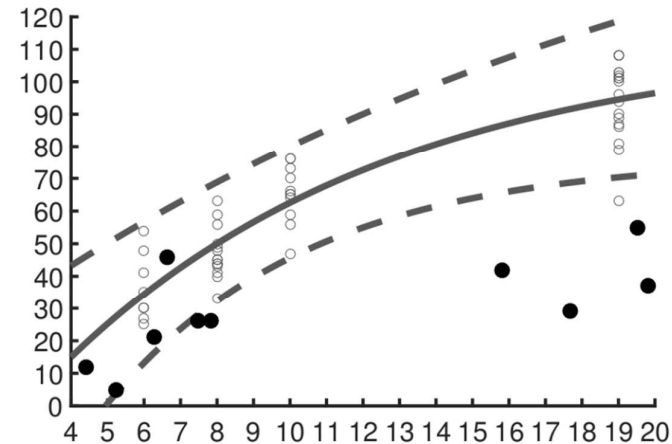


BPVS



B) Tyrosinemia III

BNT



BPVS

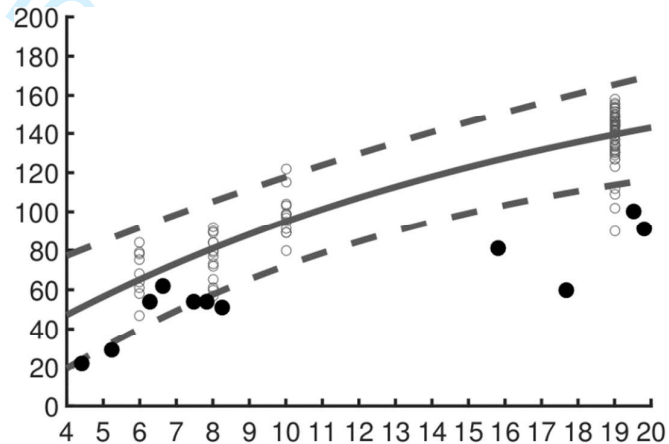


Figure 6. Boston Naming Test (BNT; production) and British Picture Vocabulary Scale (BPVS; comprehension) scores for (A) MPS-IVa and (B) Tyrosinemia III individuals and controls. Patients are filled circles and typically-developing controls are open circles. Typically developing trajectories (solid line) and 95% prediction intervals are included (dashed lines).

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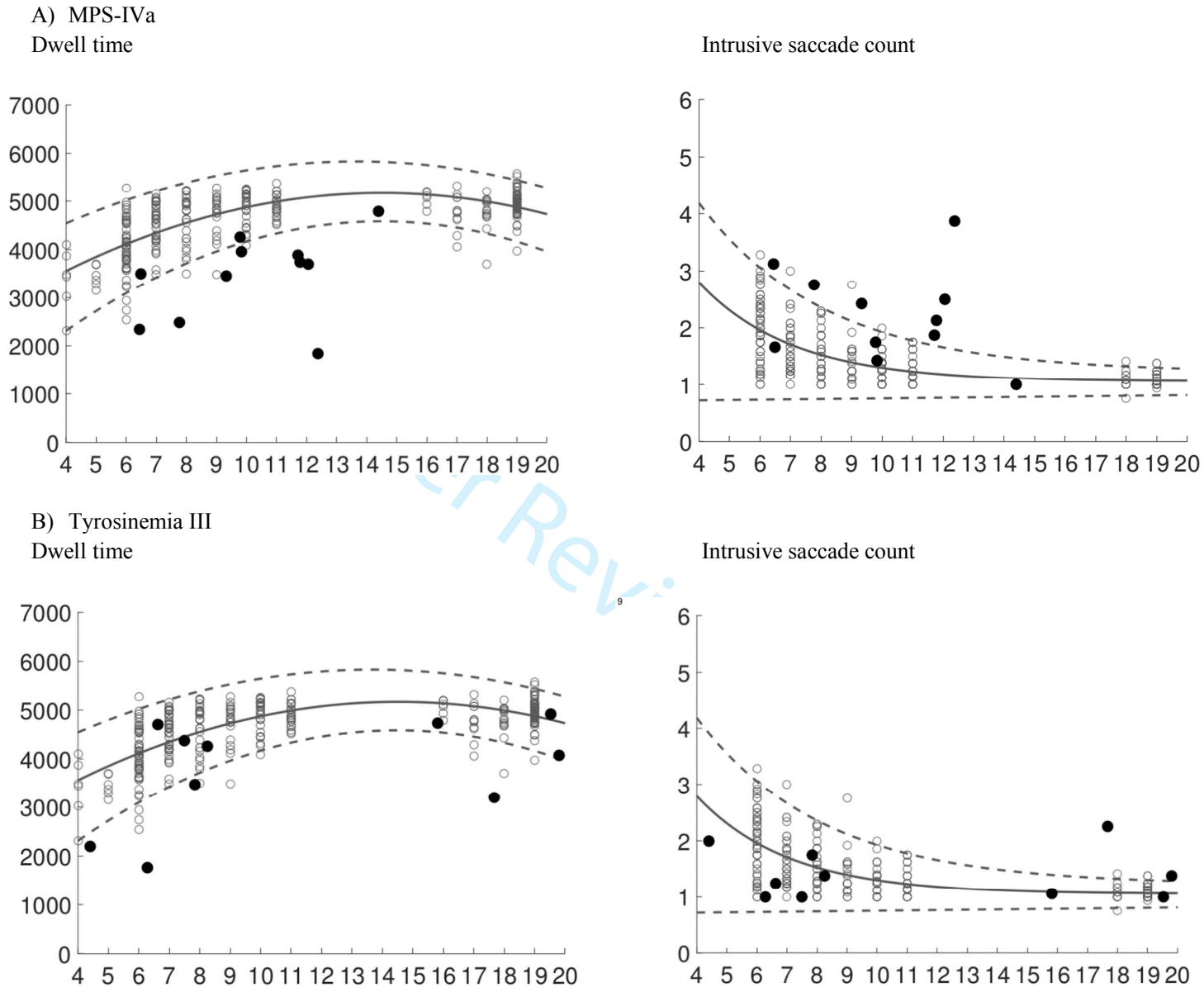
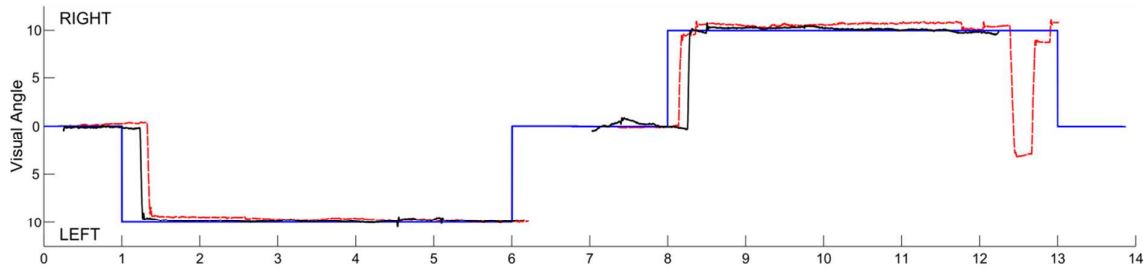


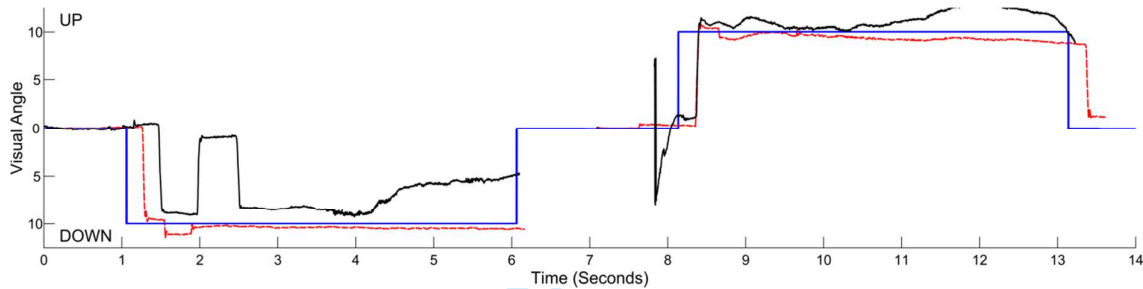
Figure 7. Fixation dwell time and intrusive saccade counts for (A) MPS-IVa and (B) Tyrosinemia III individuals (filled circles) and TD controls (open circles). Typically developing trajectories (solid line) and 95% prediction intervals (dotted lines) are included. Measures are collapsed across target locations.

MORQUIO SYNDROME : PATIENT 7

HORIZONTAL TARGETS

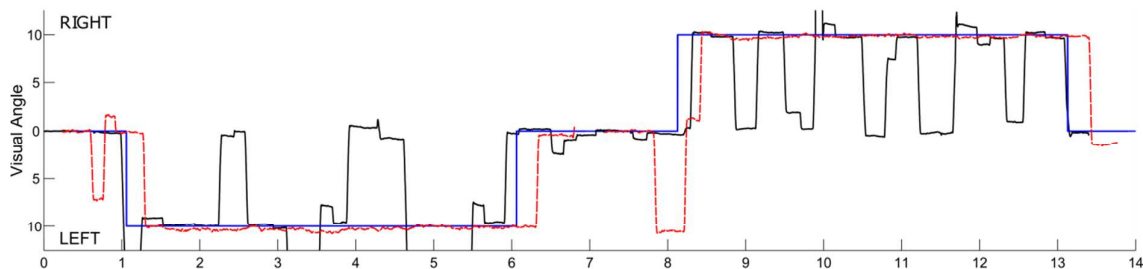
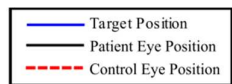


VERTICAL TARGETS



MORQUIO SYNDROME : PATIENT 11

HORIZONTAL TARGETS



VERTICAL TARGETS

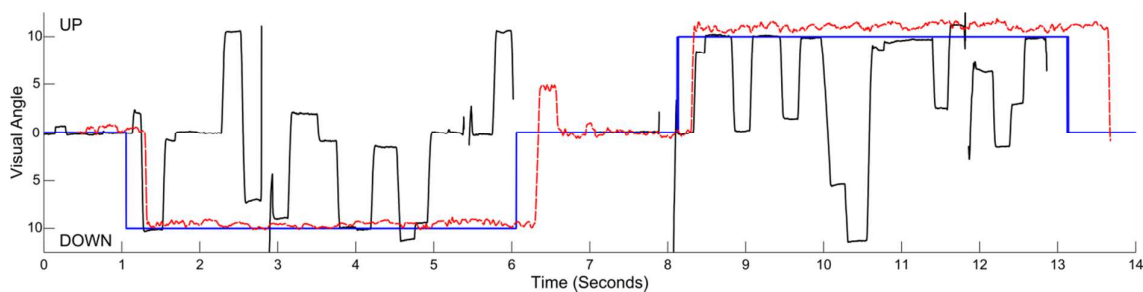


Figure 8. Example eye-movement records showing fixation time and intrusive saccades for MPS-IVa patients 7 and 11. The visual stimulus (blue line) is presented along with eye position of the patients (black line) and age-matched TD controls (red dashed line). Both patients showed fixation duration deficits but only patient 11 displayed an elevated intrusive saccade count. Patient 7 disengages before the end of the trial.

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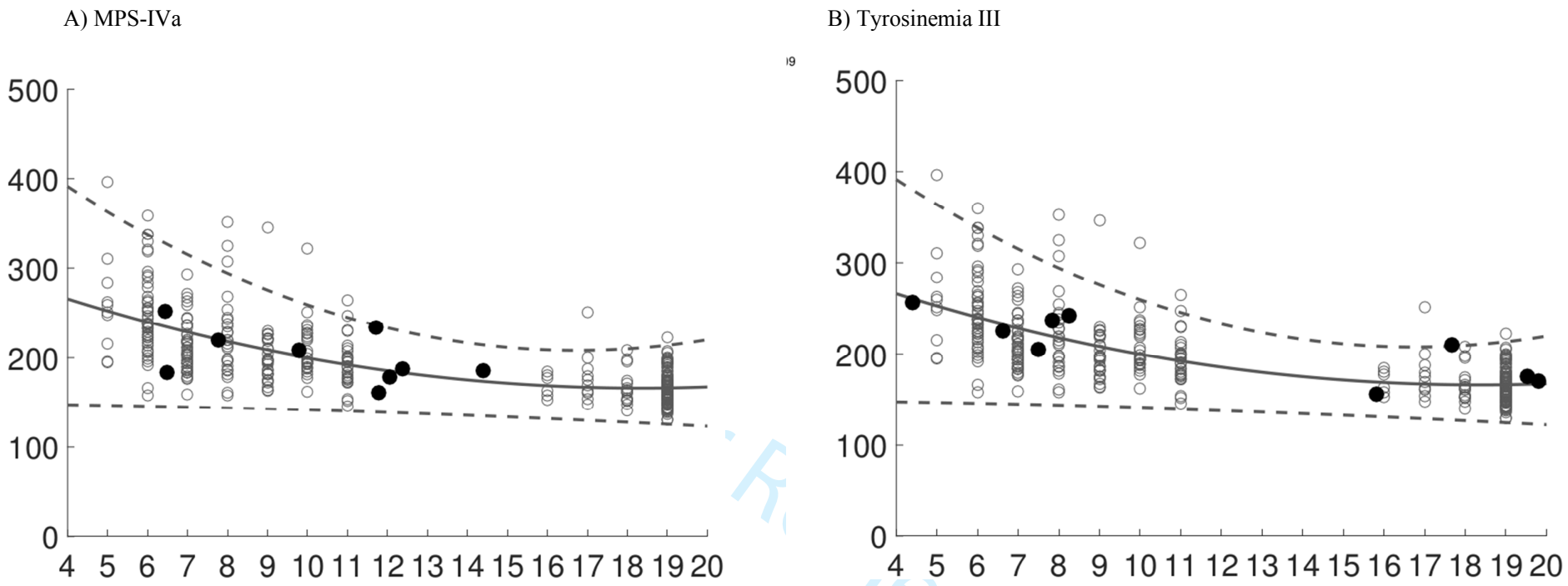


Figure 9. Average saccadic onset time for (A) MPS-IVa and (B) tyrosinemia III individuals (black dots) and TD controls (outlined grey dots). Typically developing trajectories (solid line) and 95% prediction intervals (dotted lines) are included. Onset times are collapsed across target locations.

Appendices

Appendix 1. MPS-IVa and Tyrosinemia III patient demographics

Group	PID	Gender	CA (Years)	BPVS MA (Years)	Linguistic Profile
MPS-IVa	1	M	5.27	4.02	BL – English / Pashto
MPS-IVa	2	F	6.44	5.00	BL – English / Pashto
MPS-IVa	3	F	6.48	5.07	BL – Pashto / English
MPS-IVa	4	M	7.77	8.02	BL – English / Pashto
MPS-IVa	5	F	9.33	8.07	BL – Pashto / English
MPS-IVa	6	F	9.79	10.08	ML – English
MPS-IVa	7	M	9.84	7.07	BL – Mandarin / English
MPS-IVa	8	M	10.28	7.06	BL – Pashto / English
MPS-IVa	9	M	11.71	15.10	ML - English
MPS-IVa	10	M	11.78	7.10	ML - English
MPS-IVa	11	F	12.05	11.04	BL – English / Pashto
MPS-IVa	12	M	14.39	11.03	BL – English / Pashto
T3	1	F	4.42	5.32	BL – English / Pashto
T3	2	M	5.23	3.08	BL – Pashto / English
T3	3	F	6.28	5.32	BL – English / Punjabi
T3	4	M	6.62	9	ML - English
T3	5	F	7.48	5.92	BL – English / Pashto
T3	6	F	7.83	5.00	BL – Pashto / English
T3	7	M	8.25	2.92	BL – English / Pashto
T3	8	M	15.81	5.32	BL – English / Pashto
T3	9	M	17.68	7.92	BL – Pashto / English
T3	10	F	19.52	6.08	BL – English / Punjabi
T3	11	F	19.81	10.32	BL – English / Punjabi

Note: ML, Monolingual, BL, Bilingual

Appendix 2. MPS-IVa model results.

Model	AIC	Δ AIC	Akaike Weight
Simple RT			
Generating model: <i>Condition X Age² X Group</i>			
Random effects structure: <i>(1 Participant) + (1 Age)</i>			
Condition X Age ² + Age ² X Group	-458.7	0.0	0.23
Condition X Age ² + Group	-458.7	0.0	0.22
Condition X Age ²	-458.5	0.2	0.20
Condition X Age ² + Age ² X Group + Condition X Group	-455.8	2.8	0.05
Condition X Age ² + Condition X Group	-455.8	2.9	0.05
Age ² X Group	-455.4	3.3	0.04
Feature search			
Generating model: <i>Display Size X Age X Group</i>			
Random effects structure: <i>(1+Display Size Participant)</i>			
Age + Group	3182.2	0.0	0.24
Display Size + Age + Group	3182.5	0.3	0.20
Group X Age	3183.6	1.4	0.12
Display Size X Age + Group	3183.7	1.5	0.11
Age X Group + Display Size	3183.9	1.7	0.10
Display Size X Group + Age	3184.5	2.3	0.07
Display Size X Age + Group X Age	3185.1	2.9	0.06
Display Size X Age + Display Size X Group	3185.7	3.5	0.04
Conjunction search			
Generating model: <i>Display Size X Age X Group</i>			
Random effects structure: <i>(1 + Display Size Participant)</i>			
Display Size X Age + Group X Age	5539.5	0.0	0.19
Display Size + Age X Group	5539.5	0.0	0.19
Display Size X Age + Group	5540.2	0.8	0.13
Display Size + Age + Group	5540.3	0.8	0.13
Display Size X Age + Group X Age + Display Size X Group	5541.3	1.8	0.08
Display Size X Age X Group	5543.1	3.6	0.03
Boston Naming Test			
Generating model: <i>Age X Group</i>			
Age	560.5	0.0	1.00
Age X Group	829.3	268.8	0.00
British Picture Vocabulary Scale			
Generating model: <i>Age X Group</i>			
Age X Group	829.3	0.0	0.53
Age + Group	830.0	0.7	0.38
Age	833.0	3.6	0.09
Group	1004.8	175.5	0.00

Fixation dwell timeGenerating model: *Condition X Age² X Group*Random effects structure: *(1|Participant)*

Condition X Age ² + Age ² X Group + Condition X Group	16713.0	0.0	0.52
Condition X Age ² X Group	16714.1	1.2	0.29
Condition X Age ² + Condition X Group	16715.0	2.1	0.18
Condition X Age ² + Age ² X Group	16721.7	8.8	0.01

Intrusive saccadesGenerating model: *Condition X Age² X Group*Random effects structure: *(1|Participant)*

Condition X Age ² + Group	1734.9	0.0	0.29
Condition X Age ² + Condition X Group	1735.1	0.3	0.26
Condition X Age ² + Age ² X Group	1736.0	1.1	0.17
Condition X Age ² + Age ² X Group + Condition X Group	1736.1	1.2	0.16
Condition X Age ² X Group	1738.2	3.3	0.06

Saccade onsetGenerating model: *Condition X Age X Group*Random effects structure: *(1|Participant)*

Condition X Age + Condition X Group	-977.0	0.0	0.58
Condition X Age + Age X Group + Condition X Group	-975.0	2.0	0.21
Condition X Age	-972.8	4.2	0.07

Saccade velocityGenerating model: *Condition X Age X Group*Random effects structure: *(1|Participant)*

Condition X Age	15446.6	0.0	0.63
Condition X Age + Group	15448.5	2.0	0.24
Condition X Age + Age X Group	15450.2	3.7	0.10

Appendix 3. Tyrosinemia III model results.

Model	AIC	Δ AIC	Akaike Weight
Simple RT			
Generating model: <i>Condition X Age² X Group</i>			
Random effects structure: <i>(1 Participant)</i>			
Condition X Age ² X Group	-422.1	0.00	0.45
Age ² + Group	-420.1	1.97	0.17
Age ² + Group + Condition	-419.5	2.60	0.12
Age ² X Group	-418.5	3.63	0.07
Feature search			
Generating model: <i>Display Size X Age X Group</i>			
Random effects structure: <i>(1 + Display Size Participant)</i>			
Age X Group	3232.2	0.0	0.29
Group X Age + Display Size X Group	3233.1	0.9	0.18
Display Size + Group X Age	3233.2	1.1	0.17
Display Size X Age + Group X Age + Display Size X Group	3233.7	1.6	0.13
Display Size X Age + Group X Age	3233.8	1.6	0.13
Display Size X Age X Group	3235.4	3.2	0.06
Conjunction search			
Generating model: <i>Display Size X Age X Group</i>			
Random effects structure: <i>(1 + Display Size Participant)</i>			
Display Size + Age + Group	5565.7	0.00	0.18
Display Size + Age X Group	5565.8	0.07	0.17
Display Size X Age + Group	5566.5	0.81	0.12
Display Size X Age + Group X Age	5566.6	0.87	0.11
Display Size X Group + Age	5567.2	1.47	0.09
Group X Age + Display Size X Group	5567.2	1.52	0.08
Display Size + Age	5568.0	2.29	0.06
Display Size X Age + Group X Age + Display Size X Group	5568.0	2.31	0.06
Display Size X Age X Group	5568.7	2.97	0.04
Display Size X Age	5568.8	3.08	0.04
Boston Naming Test			
Generating model: <i>Age X Group</i>			
Age X Group	532.6	0.0	0.93
Age + Group	537.8	5.2	0.07
Age	566.4	33.8	0.00
Group	593.9	61.4	0.00
British Picture Vocabulary Scale			
Generating model: <i>Age X Group</i>			
Age X Group	807.3	0.0	0.93

Age + Group	812.5	5.2	0.07
Age	876.6	69.3	0.00
Group	975.7	168.4	0.00

Fixation dwell timeGenerating model: *Condition X Age² X Group*Random effects structure: *(1|Participant)*

Condition X Age ² + Condition X Group	16009.9	0.0	0.34
Condition X Age ² X Group	16010.2	0.3	0.29
Condition X Age ² + Group	16011.2	1.3	0.18
Condition X Age ² + Age ² X Group + Condition X Group	16011.9	2.0	0.13
Condition X Age ² + Age ² X Group	16013.2	3.3	0.07

Intrusive saccadesGenerating model: *Condition X Age² X Group*Random effects structure: *(1|Participant)*

Condition X Age ² + Age ² X Group	1645.5	0.0	0.29
Condition X Age ²	1645.6	0.0	0.28
Condition X Age ² X Group	1646.9	1.4	0.15
Condition X Age ² + Group	1647.4	1.9	0.11
Age ² + Condition	1649.2	3.7	0.05

Saccade onsetGenerating model: *Condition X Age X Group*Random effects structure: *(1|Participant)*

Condition X Age	-975.4	0.0	0.51
Condition X Age + Group	-974.1	1.3	0.26
Condition X Age + Age X Group	-972.1	3.3	0.10

Saccade velocityGenerating model: *Condition X Age X Group*Random effects structure: *(1|Participant)*

Condition X Age + Condition X Group	15455.0	0.0	0.36
Condition X Age	15455.8	0.8	0.24
Condition X Age + Group	15456.2	1.2	0.19
Condition X Age + Age X Group + Condition X Group	15457.0	2.0	0.13
Condition X Age + Age X Group	15458.2	3.2	0.07
