

**TASK SWITCHING DEFICITS AND REPETITIVE BEHAVIOUR IN GENETIC
NEURODEVELOPMENTAL DISORDERS: DATA FROM CHILDREN WITH
PRADER-WILLI SYNDROME CHROMOSOME 15 Q11-Q13 DELETION AND
BOYS WITH FRAGILE-X SYNDROME**

Kate A. Woodcock, Chris Oliver, Glyn W. Humphreys

School of Psychology
University of Birmingham
Birmingham
B15 2TT, UK

Corresponding author:

Kate A. Woodcock
University of Birmingham
papers@katewoodcock.com
Tel: (+44) 121 414 2942
Fax: (+44) 121 414 4897

Short title: Cognition and behaviour in genetic syndromes

The manuscript was published in *Cognitive Neuropsychology* in 2009. The final version can be accessed here: Woodcock, K. A., Oliver, C., & Humphreys, G. W. (2009). Task switching deficits and repetitive behaviour in genetic neurodevelopmental disorders: Data from children with Prader-Willi syndrome chromosome 15 q11-q13 deletion and boys with Fragile-X syndrome. *Cognitive Neuropsychology*, 26, 172-194. doi: 10.1080/02643290802685921

ABSTRACT

Prader-Willi (PWS) and Fragile-X syndromes (FraX) are associated with distinctive cognitive and behavioural profiles. We examined whether repetitive behaviours in the two syndromes were associated with deficits in specific executive functions. PWS, FraX and typically developing (TD) children were assessed for executive functioning using the Test of Everyday Attention for Children and an adapted Simon spatial interference task. Relative to the TD children, children with both PWS and FraX showed greater costs of attention switching on the Simon task, but after controlling for intellectual ability, these switching deficits were only significant in the PWS group. Children with PWS and FraX also showed significantly increased preference for routine and differing profiles of other specific types of repetitive behaviours. A measure of switch cost, from the Simon task, was positively correlated to scores on preference for routine questionnaire items, and strongly associated with scores on other items relating to a preference for predictability. It is proposed that a deficit in attention switching is a component of the endophenotypes of both PWS and FraX and is associated with specific behaviours. This proposal is discussed in the context of neurocognitive pathways between genes and behaviour.

INTRODUCTION

Prader-Willi syndrome (PWS) is a genetic disorder with a population prevalence rate of at least 1:52 000 (lower bound estimate) and a gender ratio of 1:1 (Whittington et al., 2001). There are two principal genetic causes of PWS: a paternal deletion within the chromosome 15 q11-q13 region (60-70%) or maternal uniparental disomy (UPD) of chromosome 15 (25-30%). Chromosomal translocations or mutations of the imprinting centre also account for a small number of cases (Boer et al., 2002). PWS is associated with intellectual disability and one general effect of the PWS genotype appears to be a downwards shift of the distribution of IQ scores by approximately 40 points (Whittington et al., 2004a). Additionally, evidence supports a distinct pattern of cognitive strengths and weaknesses in the syndrome: relative strengths in academic achievement (Whittington et al., 2004 b) and visual processing (Dykens, 2002), and weaknesses in auditory processing (Stauder, Brinkman & Curfs, 2002), mathematical skills (Bertella et al., 2005), and short-term memory (Walley & Donaldson, 2005).

Fragile X syndrome (FraX) is the most common hereditary cause of intellectual disability (1:4000 live births in males and 1:8000 in females; Turner, Webb, Wake & Robinson, 1996), caused by a mutation in a single gene on the X chromosome and the resulting failure of FMR-1 protein transcription (Siomi, Siomi & Nussbaum, 1993). Gender differences in expression of FraX arise due the X-linked nature of the syndrome (Loesch, Huggins & Hagermann, 2004). Males with full mutation FraX (>200 CGG repeats) generally show greater intellectual disability than females (moderate-severe vs. none-mild: Alanay et al., 2007; Riddle et al., 1998). Individuals with FraX show strengths in verbal relative to performance IQ and in simultaneous relative to sequential

processing. Additionally, there are specific deficits in short-term memory for complex sequential information relative to that for simple, meaningful information, and in visuo-construction and visuo-spatial skills relative to visuo-perceptual integration and face-emotion recognition (Cornish, Sudhalter & Turk, 2004).

Frequent repetitive behaviours form a component of the behavioural phenotypes associated with both PWS and FraX (Feinstein & Reiss, 1998; Holland et al., 2003). In PWS this behaviour is characterized by insistence on sameness in daily routines, hoarding, repetitive phrases or questions, ordering, cleaning and repetitive skin picking (Clarke et al., 2002; Greaves, Prince, Evans & Charman, 2006; Moss, 2005; Wigren & Hansen, 2003). Repetitive behaviour in FraX, as in PWS, includes preference for routines and repetitive speech, but additionally includes stereotypical movements and repetitive self-injurious behaviour (not only skin picking) (Belser & Sudhalter, 2001; Baranek et al., 2005; Symons, Clark, Hatton, Skinner & Bailey, 2003; Moss, 2005). It has been suggested that the preference for routine is equally prevalent in both syndromes, but individuals with FraX generally show more repetitive speech, repetitive movements of the body and arranging of objects (Steinhausen et al., 2002; Moss, 2005).

The relations between the clinically apparent repetitive behaviours observed in these syndromes and possible underlying cognitive deficits has not been well characterised. Nevertheless, several authors have speculated that the repetitive behaviours may be linked to deficits in “executive functioning”. Executive functioning generally refers to cognitive processes that allow the control and regulation of behaviour (Alvarez & Emory, 2006) and is an umbrella term that includes focusing attention, inhibiting

competing responses, attention switching, planning, and updating, checking and coding the contents of working memory (Smith & Jonides, 1999).

Typically developing children show high levels of repetitive behaviours particularly when around 4 years of age (Evans et al., 1997). Pietrefesa & Evans (2007) showed that greater difficulty with inhibition on a go-nogo task and set shifting in a Stroop task was associated with higher levels of repetitive behaviours (reported by an informant) in 4-6 year olds. This suggests that the decrease in normal repetitive behaviour during typical development may be associated with the development of executive function.

Autism is another developmental disorder associated with frequent repetitive behaviours (Bodfish, Symons, Parker & Lewis, 2000). Lopez, Lincoln, Ozonoff & Lai (2005) showed that repetitive behaviour in a group of high functioning individuals with autism was associated with various executive capacities, but the model that best predicted repetitive behaviour in regression analysis involved impaired cognitive flexibility with intact working memory and response inhibition. This underlines the possibility that deficits in some components of executive function, but not in others, may be associated with repetitive behaviour.

Repetitive behaviours are also commonly shown in individuals with dementia. Cullen et al., (2005) employed direct cognitive assessments and informant report measures to investigate repetitive behaviour, memory and executive functioning in participants with Alzheimer's disease. Executive dysfunction predicted the presence of repetitive statements, stories and actions, and repetitive actions were associated with performance on a direct assessment of inhibition and attentional switching. Other classes of

repetitive behaviour however, were not associated with any of the measures of executive functioning highlighting the possibility that executive dysfunction may underlie particular classes of repetitive behaviour but not others.

It is unclear from this evidence which (if any) particular executive processes are critical in the development of repetitive behaviour. In addition, executive processes may themselves be multi-componential and these components could selectively dissociate. Attention switching for example appears to require both the inhibition of a prior task and the re-configuring of a new task-set (set of responses associated with a particular task; e.g. Rogers & Monsell, 1995). The study of switching in patients with brain lesions has provided evidence for the involvement of different critical brain regions in each of these components (Aron, Monsell, Sahakian & Robbins, 2004).

It is also unclear if particular executive deficits may be related to certain classes of repetitive behaviour but not others, or if the relationship between executive deficits and repetitive behaviour may also apply to PWS and FraX. Nevertheless, there is evidence that boys with FraX can show problems with inhibition and visual attention switching (Munir, Cornish & Wilding, 2000; Cornish, Munir & Cross, 2001; Wilding, Cornish & Munir, 2002) and that individuals with PWS can show problems with inhibition (Stauder et al., 2005). It is possible that such deficits play a contributory role in the repetitive behaviour shown by individuals with FraX and PWS. For example, if individuals find it difficult to inhibit the task they are doing, or difficult to re-configure cognitive processes to perform a new task, then they may tend to repeat behaviours because it is cognitively less demanding.

To address these issues we report a first study into the ability to switch attention and to inhibit pre-potent responses in children with PWS and FraX, examined in relation to their preference for repetition in everyday life. Differences have been reported between the cognitive and behavioural profiles of people with the deletion and UPD subtypes of PWS (Stauder et al., 2005; Milner et al., 2005), and between males and females with FraX (Loesch et al., 2004). Consequently, we restricted our sample to children with the deletion subtype of PWS and boys with FraX, where problems with inhibition have previously been noted (see above). The performance of these two syndrome groups was compared to that of a group of typically developing children. Alongside measuring task switching and response inhibition, we developed repetitive behaviour profiles for each child so that we could assess the relations between repetitive behaviour and executive dysfunction. As described above, both individuals with PWS and FraX appear to show a particularly high preference for routine (e.g. Steinhausen et al., 2002). Evidence from an interview study we have recently carried out suggested that the high preference for predictability in children with PWS and FraX was associated with other behaviours including repetitive questions, temper outburst related behaviours in PWS and stereotypical movements and repetitive self-injurious behaviour in FraX (Woodcock, Oliver & Humphreys, in press). We assessed whether there was any relationship between a particular executive deficit and this preference for predictability.

METHOD

Participants

The participants were 28 children with the paternal deletion subtype of PWS, 28 boys with FraX with a full FMR1 mutation, and 28 typically developing children. Informed

consent from parents and carers, and assent from children to participate was obtained. Twelve males and sixteen females with PWS recruited via the Prader-Willi Syndrome Association-UK, aged between 6:10 and 18:7 years, with a mean age of 13:5; SD: 3:3. Boys with FraX were recruited via the Fragile-X Society, aged between 9:2 and 19 years, with a mean age of 13:11; SD: 2:6. Typically developing children were eleven males and seventeen females recruited via primary schools, aged between 5:1 and 11:9 years, with a mean age of 8:8; SD 1:11. Most participants in all groups were of White Caucasian ethnic origin and of moderate to high socio-economic status. Individuals were recruited if they lived within three hours from the research base, had a genetically confirmed classification of their diagnosis (PWS and FraX groups) and were aged between 6 and 19 years in the syndrome groups or 5 and 12 years in the typically developing group. Additionally, from 30 appropriate individuals with PWS and 33 with FraX, 28 were selected to match the number of typically developing children based on performance on the *Wechsler Intelligence Scales for Children* (described below).

Measures

We took standardised measures of cognitive function based on the *Wechsler Intelligence Scales for Children (WISC-III)* (Wechsler, Golombok & Rust, 1992) and the *Test of Every Day Attention for Children* (Manly, Robertson, Anderson & Nimmo-Smith, 1999). A recognised short form of the WISC was administered (e.g., Mason, Humphreys & Kent, 2003) using the similarities, vocabulary, block design and object assembly subscales. This was done even with the older participants since the tests remained within their intellectual range. Four TEACH subtests were given: each task chosen to assess specific aspects of executive functioning. *Sky Search* was chosen as a

measure of selective attention. Participants searched for targets among distractors. Dependent variables were the number of targets identified, the mean time taken to identify a single target, and a selective attention score that was calculated by subtracting the time-per-target in a similar motor control task (no distractors) from the time-per-target in the experimental task. *Sky Search DT* was selected as a measure of the ability to divide attention. Participants completed a second *Sky Search* task while reporting the number of tones counted in an auditory task. The dependent variable (dual task decrement score) was the mean time per visual target divided by the proportion of counting items correct, with the *Sky Search* time per target subtracted from this. The *Walk Don't Walk* task provided a measure of sustained attention and requires the unpredictable suppression of responses. Participants had to mark steps along twenty paths when one tone was presented, but stop when a different tone was presented. The dependent variable was the number of paths marked correctly. Finally, the *Opposite Worlds* task was included as a measure of attentional control. Participants were presented with a string of "1" and "2" digits and were required to read the digits as they normally would (*same world*), or say the number corresponding to the opposite digit (*opposite world*). Dependent variables were the time taken to complete each condition, and an attentional control score calculated by subtracting the *same world* time from the *opposite world* time (e.g. Munir et al., 2000).

Response inhibition and task switching were assessed on a variant of the Simon spatial interference task (Simon, 1969). On each trial a red square or a blue circle was presented to one side of the participant's visual field on a computer screen. There were two different response options made using a computer keyboard (Z and M keys marked with stickers): a left side, red square key and a right side, blue circle key. Two types of

task required responses to either i) the location of the stimulus, or ii) the identity of the stimulus. Each task included both congruent trials (red square on the left or blue circle on the right) and incongruent trials (red square on the right or blue circle on the left). Response interference is demonstrated when incongruent responses are slower/ less accurate than congruent responses (the congruency effect), increases in response interference indicate less effective response inhibition.

To measure task switching (from the location to the identity task, and vice versa), trials were presented in either a single task block (32 trials of the same task: eight of each picture in each location) or in a mixed task block (36 trials). Trials within mixed task blocks followed a predictable task sequence with eight trials of one task type followed by a task switch (indicated by a verbal and written instruction), repeated for the first 32 trials, and followed by four trials of the final task type. This resulted in four task switches within each mixed task block. Comparison of the trials following a task switch (switch trials) and trials preceding a task switch (no-switch trials) gave a measure of the difficulty associated with task switching.

We also included clinical measures of repetitive behaviour. The *Repetitive Behaviour Questionnaire (RBQ)* (Moss & Oliver, 2008) is an informant report questionnaire in which participants rate the frequencies of nineteen observable, operationally defined repetitive behaviours on a scale of 0-4 (never, once a month, once a week, once a day, more than once a day). Previous studies have shown strong inter-rater reliability across individuals with heterogeneous causes of intellectual disability, high test-retest reliability and strong concurrent validity e.g. there is a strong association between pairs of scores referring to the same behaviour on the RBQ and the Repetitive Behaviour

subscale of the Autism Screening Questionnaire (Moss & Oliver, 2008). The *Childhood Routines Inventory* (Evans et al., 1997) requires participants to rate the frequencies of nineteen observable behaviours on a scale of 1-5 (never, a little, sometimes, quite a lot or very much). This measure has previously been used with normative samples of children between 8 and 72 months (Evans et al., 1997), in children with Down syndrome (Evans & Gray, 2000), in people with autism, and in people with PWS (Greaves et al., 2006).

Procedure

Participants were tested in homes or schools or in Birmingham University. Questionnaire measures were administered verbally to parents and carers. Test sessions began with administration of the Simon task, followed by the TEACH and WISC tests, administered according to their manuals. During the Simon task participants sat approximately 50cm away from the computer screen. On each trial a central fixation cross (1000ms) appeared followed by the stimulus, which remained until the response. Following a response, a blank screen replaced the display and the next trial began after 500ms. Initially two single task blocks were presented: one block of each task type, with the order counterbalanced across participants. These were followed by one mixed task block in which the type of task presented first was counterbalanced across groups of participants who completed each type of single task block first. Practise sessions were presented before each block to ensure that each child understood what was required (each practise session involved eight trials and each participant completed enough sessions (1-3) so that they responded correctly on at least 6 out of the 8 trials).

RESULTS

Part I: Executive functioning and repetitive behaviour profiles in children with PWS and boys with FraX

Intellectual Ability and Age

Due to inability or unwillingness to remain in the testing situation for long enough, only 19 of the boys with FraX completed the similarities WISC subscale, 20 completed the object assembly and 21 the block design. Paired t-tests showed that on all subtests, the typically developing group scored significantly higher than the two syndrome groups (despite being 5 years younger on average) and the PWS group scored significantly higher than the FraX group (see Appendix A). In order to control for intellectual disability we therefore treated raw scores on the WISC Vocabulary scale (mean (SDs): PWS: 17.14 (7.13), FraX: 10.29 (3.60) and TD: 28.46 (9.84)) as a covariate in all future analysis. Vocabulary score was used in this way as it is likely to be least affected by the executive processes we were measuring. As expected, the syndrome groups differed significantly from the TD group in chronological age (TD>PWS; $t(54)=6.77$, $p< .001$, TD>FraX; $t(54)=8.99$, $p< .001$), however there was no significant difference between the chronological ages of the two syndrome groups ($t(54)= 0.68$, $p= .50$). Chronological age was therefore also treated as a covariate in order to control for the amount of life experience.

TEACH

Due to lack of understanding, unwillingness or inability to remain in the testing situation for long enough, one child with PWS did not complete the *Sky search* and *Sky search DT* subtests of the TEACH and only twenty of the boys with FraX completed the *Sky search*, sixteen completed the *Sky search DT*, nineteen completed the *Walk don't walk* and 23 completed the *Opposite Worlds* tasks. Means and standard deviations for the performance of each group on the TEACH subtests are shown in Table 1.

[Table 1]

To investigate if executive deficits were apparent in children with PWS and FraX and if the profile of executive deficits differed between the syndrome groups, profiles of executive functioning measured by the TEACH were compared between the syndrome groups and the TD group. Group differences were analysed using mixed effects ANCOVAs with group as the between subjects factor and the within subjects factor (TEACH) comprising one level for each of the eight TEACH dependent variables.¹ Group differences between individual executive processes were examined using multivariate ANCOVAs with group as the fixed factor and each dependent variable from the TEACH as a separate between subjects factor: this method is equivalent to carrying out eight separate one-way ANOVAs and therefore a corrected significance level of $p \leq .01$ was applied.

¹ The effect of gender on TEACH performance was examined within PWS and TD groups with an additional between subjects *gender* (male, female) factor. However there were no significant main effects of gender or interactions involving gender.

Taken together, the TEACH data (eight separate dependent variables) reveal that there were overall differences between the PWS and TD groups; $F(1,62)=11.58, p=.001$, and between the FraX and TD groups; $F(1, 45)=5.04, p=.03$ in their profiles of executive functioning. There was however, no overall difference between the PWS and FraX groups ($F(1,45)=0.64, p=.45$), but separate multivariate ANCOVAs considering only i) PWS and TD groups and ii) FraX and TD groups, showed different profiles for the PWS and FraX groups across the subtests. The children with PWS showed problems with selective and divided attention (in the *Sky Search* and the *Sky Search DT*), while the boys with FraX showed problems with the *Walk Don't Walk* task (requires sustained attention and response inhibition). Neither group showed particular problems in generating opposite names for digits when comparing performance on the two sections of the *Opposite Worlds* task.

Simon task

Only reaction times (RTs) for correct response trials were analysed (shown in Table 2). There were large group differences in the overall mean RTs ($F(2,83)=19.18, p<.001$), which would make it difficult to interpret absolute differences in the effects of congruency and switching on RTs across the groups. For example; a greater RT cost of switching (increase in RT between non-switching and switching trials) in one of the syndrome groups relative to the TD group, may actually result from a mean RT in switching trials that was increased by the same factor in both groups relative to non-switching trials. For this reason we computed standard scores (z-values) for the mean RTs in each trial/ task type. Standard scores indicate the distance in standard deviation units between a score and the population mean (the score minus the mean score for the

population, divided by the standard deviation of scores in that population). So, for example to calculate the standardised RTs for identity congruent trials in single task blocks for participants in the PWS group, we subtracted the overall mean RT in single task blocks (all trial/ task types) for the PWS group, from the participants' mean RTs for identity, congruent, single task block trials, and divided this by the standard deviation of overall mean RTs in single task blocks in the PWS group (see Appendix B). For accuracy analysis, considering the binomial distribution of accuracy data, the proportions of correct responses were transformed using an arcsine transformation (inverse sine of the square root of the value) in order to increase the normality of the data (Chang, 2006). Data were analysed using a series of mixed effects ANCOVAs for single and mixed task blocks separately.

[Table 2]

Single task blocks

The ANCOVAs for single task blocks included group as the between subjects factor, and congruency (congruent, non-congruent) and task type (identity, location) as within subjects factors.² For standardised RTs, the ANCOVA considering all three groups showed no significant main effects of group or interactions including group. The ANCOVA of arcsine transformed accuracy data considering all three groups showed a significant group*task interaction; $F(2,79)=9.88$, $p < .001$, but no significant interactions between group and congruency. The group*task interaction was further investigated between each pair of groups and remained significant in all comparisons. These

² The effect of gender on performance in single task blocks of the Simon task was examined within PWS and TD groups with an additional between subjects *gender* (male, female) factor. However there were no significant main effects of gender or interactions involving gender.

interactions resulted from a significant accuracy advantage for the location task over the identity task in the TD group ($t(27) = -3.50, p = .002$), but the reverse effect in PWS ($t(27) = 2.56, p = .01$) and FraX groups ($t(27) = 6.68, p < .001$). Thus the groups showed differences in performance across the two task types in single task blocks, but there were no significant group differences in the effect of congruency on performance, and so no evidence for group differences in response interference.

Mixed task blocks

Performance in mixed task blocks was analysed in the same way as performance in single task blocks, except for an additional within subjects switch factor (switch, non-switch).³ The mean RT when switching was that of the four trials following each switch, while the mean RT when not switching was that of the four trials preceding each switch. The first four trials of mixed task blocks were not included in the analysis of switching. The ANCOVA of standardised RTs across all three groups showed significant task*group; $F(2,79) = 5.25, p = .007$ and switch*group $F(2,79) = 3.53, p = .034$ interactions. The congruency*group interaction was not significant and neither were any of the higher level interactions with group. The significant interactions were further investigated between each pair of groups. For the comparison between the PWS and TD groups only, both the task*group ($F(1,52) = 6.95, p = .011$) and switch*group ($F(1,52) = 7.36, p = .009$) interactions remained significant, however switch and group also interacted significantly with congruency ($F(1,52) = 4.24, p = .044$). Across FraX and TD groups, only the task*group ($F(1,52) = 4.20, p = .046$) interaction remained

³ The effect of gender on performance in mixed task blocks of the Simon task was examined within PWS and TD groups with an additional between subjects *gender* (male, female) factor. However there were no significant main effects of gender or interactions involving gender.

significant, but task and group also interacted significantly with congruency ($F(1,52)=5.86, p=.019$). In the comparison between the PWS and FraX groups neither interaction was significant.

The group*task interactions resulted from significantly decreased standardised RTs in location task trials relative to identity trials in typically developing children ($t(27)=2.74, p=.011$), but the reverse trend in children with PWS and boys with FraX. This result confirms the findings from the single task blocks (above). Across FraX and TD groups the interaction between task, group and congruency was due to an increased effect of congruency in the FraX group compared to the TD group in the location task ($t(31.90)=1.46, p=.531$), but the reverse effect (TD>FraX) in the identity task ($t(54)=-1.73, p=.090$). Taking the two sets of analyses for the atypically developing vs. the TD group, both PWS and FraX groups showed a specific deficit when performing the location task relative to identity task. In addition, in boys with FraX, this location task deficit was also associated with an increased congruency effect (reflecting increased response interference in the location task).

Relative to the TD group, children with PWS showed increased RT costs of switching across both congruent and non-congruent trials demonstrated by the significant group*switch interaction (see Figure 1). The additional interaction with congruency resulted from a greater group difference in switching to congruent trials ($F(1, 52)=12.23, p=.001$) than in switching to non-congruent trials ($F(1,52)=.781, p=.381$). A similar pattern was apparent in the FraX group, though the interaction with the TD

group was not then significant⁴. The data are indicative of greater switch costs in the atypically developing groups, particularly when switching to congruent trials, with the effects being largest for PWS individuals when differences in intellectual ability were controlled for.

[Figure 1]

The ANCOVAs performed on the arcsine transformed accuracy data across all three groups showed a significant main effect of group ($F(1,79)=7.91, p= .001$), but no significant interactions including group. There was no significant main effect of group across PWS and TD groups, but there was a reliable overall difference between the PWS and FraX groups (PWS>FraX: $F(1,52)=6.26, p= .016$), and the FraX and TD groups (TD>FraX: $F(1,52)=9.05, p= .004$). Accuracy was significantly lower in the FraX group compared to the PWS and TD groups. There were no other reliable effects. Thus the effects of switching and congruency did not impact on the accuracy of performance.

Questionnaire measures

Questionnaire scores (means and SDs can be found in Table 3 and Appendix C) were analysed using mixed effects ANCOVAs with group as the between subjects factor and behaviour class as the within subjects factor comprising one level for each of the

⁴ Across FraX and TD groups, the group*switch*congruency interaction showed a trend towards significance ($F(1,52)=2.69, p= .107$). Similar to the PWS group (see Figure 1), boys with FraX showed increased problems with switching to congruent trials ($F(1,52)=2.30, p= .135$) than to non-congruent trials when compared to the TD group ($F(1,52)= .374, p= .543$). Interestingly, when only chronological age and not WISC voc was used as a covariate, the switch*congruency*group interaction was significant in both PWS versus TD ($F(1,53)= 9.18, p= .004$) and FraX versus TD comparisons ($F(1,53)= 12.84, p= .001$).

nineteen questionnaire items. Considering the scoring of all three groups on the RBQ and CRI, there were a significant main effects of group; RBQ: $F(2,79)=6.06, p=.004$; CRI: $F(2,79)=10.30, p<.001$, and significant interactions between group and behaviour class; RBQ: $F(36, 1422)=3.40, p<.001$; CRI: $F(36, 1422)=2.38, p<.001$. The group*behaviour class interactions were significant across PWS and TD groups only for the RBQ; $F(18, 936)=3.38, p<.001$ and CRI; $F(18, 936)=3.41, p<.001$, and across FraX and TD groups only for the RBQ; $F(11.2, 581.9)=2.02, p=.024$. However, the group * behaviour class interactions were not significant when considering only PWS and FraX groups. This suggests that the children with PWS and FraX showed a profile of particularly high levels of certain classes of repetitive behaviours but not others, relative to typically developing children.

[Table 3]

Scores for individual classes of repetitive behaviour on each questionnaire were analysed using multivariate ANCOVAs, with group as the fixed factor and the nineteen questionnaire items as separate between subject factors: a corrected significance level of $p\leq .01$ was applied. Table 3 shows the interactions between group and RBQ/ CRI items in the multivariate ANCOVAs considering i) PWS and TD groups and ii) FraX and TD groups only (items associated with no significant group interactions are shown in Appendix C). The repetitive behaviour profile of children with both syndromes was characterized by significantly increased scores on items relating to preference for predictability, repetitive questions, and acting out the same thing over and over in pretend play. The PWS group showed significantly increased *just right* behaviour, *completing* behaviour, persistent habits, *insisting on having things in their place*, *eating*

food in a particular way and bedtime routines relative to the TD group. The FraX group showed significantly increased lining up or arranging objects and repetitive actions relative to the TD group.

Part II: The relations between executive deficits and repetitive behaviours.

We also examined the relations between deficits in executive function in the children and repetitive behaviours. For this analysis, switch costs were calculated by subtracting standardised mean RTs for non-switching trials from the standardised mean RTs for switching trials. Pearson's partial correlation coefficients (with age and WISC vocabulary score used as covariates) were calculated between switch cost scores and scores on items of the RBQ and the CRI.

Switch costs ranged from - .57 to 3.65 for the PWS group (mean: .49, *SD*: .83), from - .51 to 1.48 for the FraX group (mean: .30, *SD*: .44), and from - 1.01 to .85 for the TD group (mean: .18, *SD*: .35). Correlations between switch cost and RBQ and CRI questionnaire items are shown in Appendix D. At a corrected level of $p < .01$ switch costs correlated only with preference for routine ($r = .31, p = .005$) and hand stereotypy ($r = .29, p = .008$) on the RBQ. Significant to a less stringent $p < .05$ level, switch costs were correlated with preference for routine ($r = .272, p = .014$) and preferring to have things in a particular order/ certain way ($r = .218, p = .050$) on the CRI, and with completing behaviour ($r = .229, p = .038$) on the RBQ. Therefore higher switch costs were associated with higher scores on all of the behaviour items that described a preference for routine and predictability.

DISCUSSION

Measures of executive function

The children with PWS and those with FraX showed distinctive profiles of relative skill and deficit in executive processes measured on the TEACH, including some impairments compared to the typically developing children even despite IQ and CA being factored out of the analysis. In the Simon task, the children with PWS and FraX showed more pronounced switch-costs compared to the typically developing children, particularly on congruent trials. However when IQ (as well as CA) was factored out of the analysis, this difference was only significant in the children with PWS. We discuss results from the TEACH and the Simon task in turn. These results point to *particular* executive processes being disturbed in these atypically developing groups. In addition, the cognitive deficits were linked to selective aspects of repetitive behaviour. This result suggests a direct link between cognitive disabilities and the emergence of clinical behaviour in neurodevelopmental groups.

TEACH performance

The finding that the PWS and FraX groups differed in their performance profile on the TEACH is interesting, suggesting that these groups have contrasting impairments in executive processes. The primary contrast on the TEACH was between *Sky Search* tasks requiring selective and divided attention (particular impairments in the PWS group), and the *Walk Don't Walk* task that required sustained attention and response inhibition (particular impairments in the FraX group). Jauregi et al. (2007) found that individuals with PWS showed a significant deficit relative to normative population

scores in the Trail Making Test, which includes a visual search selective attention component. Although these authors did not study a comparison group, our multiple group design supports the suggestion that individuals with PWS may show a specific deficit in selective attention. The *Walk Don't Walk* test has been administered previously to boys with FraX (Munir et al., 2000), who showed deficient performance relative to boys with Down syndrome and typically developing boys of equivalent mental age.

In a large sample of typically developing children, Manly et al. (2005) used structural equation modelling to show that the children's performance on the TEACH subtests could best be explained using a three-factor model of attention that distinguished between selective attention (including *Sky Search*), sustained attention (including *Walk Don't Walk*) and attentional control (including *Opposite Worlds*). Therefore, selective deficits shown by our participants appeared to be confined to the selective attention factor in children with PWS and the sustained attention factor in boys with FraX. Neither group showed particular deficits in attentional control (*Opposite Worlds*), suggesting that this executive process at least, is not selectively affected in either of the syndromes.

Simon task

Performance on single task blocks of the Simon task did not suggest any significant group differences in the necessary response inhibition, but there were significant group differences in performance across the two types of task, which were also apparent within mixed task blocks. We have explored the apparent specific deficit in location

task (relative to identity task) performance in the children with PWS and boys with FraX elsewhere (Woodcock, Humphreys & Oliver, in press). These results are in line with previously reported specific deficits in the visual processing of position information for action in males with FraX (Kogan et al., 2004). Given that the location task here can be associated with activation of the dorsal visual stream (Schumacher, Cole & D'Esposito, 2007), the data fit with proposals that the dorsal processing stream is particularly vulnerable to impairment in neurodevelopmental disorders (Braddick, Atkinson, Wattam-Bell, 2003).

The main finding from mixed task blocks in the Simon task was the significant deficit in switching attention in children with PWS and FraX, relative to the typically developing children, evident in the reaction time data. These task switching costs were particularly pronounced when the children were switching to a trial that required a congruent (verses an incongruent) response. In studies with normal adults, costs of task switching have been found to increase when participants switch to the easier of two tasks, compared to when they switch to the more difficult task (Allport, Styles & Hsieh, 1994; Rogers & Monsell, 1995). This asymmetric switch cost is associated with participants inhibiting a strong stimulus-response mapping in order to enable a weaker stimulus-response mapping (e.g., from a different dimension of the same stimulus) when task demands change and a task switch is required: Then, when participants are required to switch back to the task with the stronger stimulus-response mapping they must overcome this inhibition. Accordingly, our data suggest that the children with PWS and FraX were better able to inhibit a strong but task-inappropriate stimulus-response mapping (switching to incongruent trials with weak stimulus-response mapping was less impaired), than they were able to re-engage that strong stimulus-response mapping

following a task switch (greater difficulty in switching to congruent trials). The children with PWS and FraX may therefore show particular problems with 're-configuring' a task set to enable them to carry out an inhibited task.

If, as it seems, children with PWS and FraX show a specific deficit in task-set re-configuration, it is possible that this deficit is associated with abnormality of function in particular brain regions. Lesion studies with animals have shown that areas of the Prefrontal Cortex and the Anterior Cingulate Cortex appear to be involved in task switching (Dias, Robins & Roberts, 1996; Rushworth, Hadland, Gaffan & Passingham, 2003). Imaging studies in humans have supported the importance of these areas in task switching (e.g., Derfuss, Brass, Neumann & von Cramon, 2005), and have begun to fractionate task switching into distinct component processes (e.g., cue-related processing, preparation for a switch, target-related processing, conflict resolution) linked to different neural correlates (e.g., Ruge et al., 2005; Forstmann, Brass, Kock & von Cramon, 2005; Woodward, Ruff & Ngan, 2006). Future brain imaging studies with individuals with PWS and FraX would make an interesting contribution to this research, as well as help to identify neural correlates of the specific genetic abnormalities associated with the syndromes.

Our data suggest that the deficit in task switching may be more specific to children with PWS than to boys with FraX. However, Wilding et al. (2002) used a visual search in which participants were required to switch between searching for two different types of targets and found that boys with FraX (as well as boys with Down syndrome) showed a deficit in visual attention switching relative to typically developing children. Wilding et al. controlled for intellectual ability by matching groups of participants on a measure of

receptive vocabulary (younger typically developing groups), which was different to our strategy of statistically controlling for age and a measure of verbal ability. Although group matching for intellectual ability allows the comparison of groups that would be expected to show a similar level of cognitive functioning, variation across participants within groups means that differences in intellectual ability may still impact on results. In contrast, our strategy allowed us to remove performance on a measure of intellectual ability from the analysis. Given these results, it is possible that having an intellectual disability is associated with increased problems with attention switching, but that this capacity is additionally impaired in PWS. The data suggest that the genetic abnormality in these individuals is linked to impairments in switching attention over and above deficits in intellectual function. To the best of our knowledge, this is one of the first indications of the genetic underpinnings of the ability to switch attention, particularly linked to re-configuring the task set.

Clinical Measures

Both children with PWS and boys with FraX showed more preference for predictability and more repetitive questioning compared to the typically developing children. These results are in agreement with previous research (e.g. Steinhausen et al., 2002; Holland et al., 2003; Moss, 2005). Additionally, a high level of preference for routine and predictability was shown in children with PWS and boys with FraX in our recent interview study (Woodcock & Oliver et al., in press) and this behaviour appeared to be related to repetitive questions in both groups, temper outbursts in PWS and overt displays of anxiety (involving stereotypical movement and repetitive self-injurious

behaviour) in FraX (all of these behaviours were more likely to occur following unexpected changes).

Despite the similarities between the repetitive behaviour shown by children with PWS and FraX noted above, the behaviour could also be distinguished between the two groups. The profile in the children with PWS was characterised by insistence on the sameness (e.g., liking to eat in a particular way), as well as liking to have things completed and having persistent habits. Insistence on the sameness has been reported previously in individuals with PWS (Wigren & Hansen, 2005), as has skin picking (Wigren & Heimann, 2001), which could be described as a persistent habit. The profile in the boys with FraX however, was characterised by more lining up objects and repetitive actions (previously reported by e.g., Feinstein & Reiss, 1998). A distinction has been made between low level (repetitive movements) and high level (more complex) repetitive behaviours (e.g., Turner, 1999) and it is interesting to note that the repetitive behaviour profiles in the children with PWS and FraX could be distinguished on the basis of certain low level repetitive behaviours shown in FraX but not PWS, and certain high level behaviours shown in PWS and not FraX. Both low level and high level repetitive behaviour has been reported in individuals with autism (e.g., Bodfish et al., 2000) and it has been suggested that these behaviours may be associated with distinct underlying mechanisms (e.g., Bodfish, 2004). Our results demonstrate a fractionation of the autistic repetitive behaviour profile across different genetic syndromes, providing support for the argument that different types of repetitive behaviour are associated with different underlying mechanisms.

Relations between executive functioning and clinically significant behaviours

Importantly, despite a number of significant group differences between RBQ and CRI items, only items relating to a preference for routine and predictability were correlated (either significantly or bordering significance) to a measure of switch cost, except for hand stereotypy (significant) and completing behaviour (bordering significance). Stereotypical movement (during overt anxious reactions) has been linked to a preference for predictability in boys with FraX (Woodcock & Oliver et al., in press). This suggests that one aspect comprising the endophenotype of both PWS and FraX is a deficit in the executive component of task switching and that it is this deficit that is associated with particular behaviours. We believe that this is the first time a specific deficit in an executive function (task-set re-configuration) has been directly linked to a clinical pattern of behaviour (preference for predictability) in either PWS or FraX.

Taking the current results together with previously reported evidence (Woodcock & Oliver et al., in press), we suggest a specific route between genes and clinical behaviour via cognitive functioning. We propose that a deficit in task switching occurs in children with PWS and boys with FraX downstream from the result of the PWS and FraX genotypes on the developing brain. Further to this, we suggest that the deficit in task switching gives rise to particular difficulties (including characteristic profiles of challenging behaviour) following unexpected changes in the environment (which we suggest would place a high demand on individuals' attention switching capacity). Understanding the role of cognitive functioning in behaviour would point towards exciting potential intervention strategies. Strategies aimed at improving task switching could reduce the resistance to change (and therefore also reduce the other related behaviours): an approach that would contrast with more standard behavioural treatments

of repetitive behaviours (e.g., Iwata, Dorsey, Slifer, Bauman & Richman, 1994). A similar approach has been used successfully in children with ADHD showing that training in working memory has had a positive influence on behaviour (Klingberg, Forssberg & Westerberg, 2002).

Limitations

Due to the restricted age range of the present sample, it is possible that the reported deficits in executive capacities in the children with PWS and boys with FraX may be due to a delay in the development of these capacities, rather than to specific deficits. However, if there is a developmental delay rather than a fundamental deficit in the children, then it may be possible to provide a direct test of whether any age-related improvement in executive function is causally related to a reduction in any related behaviours. We note here that in a cross-sectional study, Dykens (2004) found that there was a reduction in repetitive and maladaptive behaviour in older adults with PWS. It would clearly be of interest to assess whether this was coincident with improvements in task switching performance.

It must be noted that in addition to the theoretical reasons discussed above for using a measure of verbal ability to control for intellectual ability, logistical constraints led us to take this approach (e.g. many participants were unwilling to complete all four WISC subtests used). Using a measure of verbal ability rather than a measure of full scale IQ is potential limitation to the present findings. However, measures of verbal ability have been widely used as indicators of broader intellectual functioning (e.g. Cornish et al., 1998; Cornish et al., 2001; Munir et al., 2000).

The present research is restricted to individuals with the deletion subtype of PWS and boys with FraX. There is some evidence for a deficit in attention switching in females with FraX (Cornish & Swainson et al., 2004), but further research would be necessary to assess the degree to which the present findings can be extended within each syndrome group. Although we have suggested that a causal association exists between a deficit in attention switching and a preference for predictability, evidence from the present study is purely correlational and therefore unable to rule out the possibility that it is the behaviours shown in PWS and FraX that cause the deficit in attention switching. It is also possible that an additional factor (e.g. environmental or physiological) not considered in the present study, could be shown to underlie both the deficit in attention switching and the preference for predictability. However, the suggestions that we have made provide a potentially useful framework for future research.

REFERENCES

- Alanay, Y., Unal, F., Turanli, G., Alikasifoglu, M., Alehan, D., Akyol, U. et al. (2007). A multidisciplinary approach to the management of individuals with fragile X syndrome. *Journal of Intellectual Disability Research*, *51*, 151-161.
- Allport, D. A., Styles, E. A., & Hsieh, S. (1994). Shifting intentional set: Exploring the dynamic control of tasks. In C. Umiltà & M. Moscovitch (Eds.), *Attention and performance XV* (pp. 421-451). Cambridge, MA: MIT Press.
- Alvarez, J. A. & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychology Review*, *16*, 17-42.
- Aron, A. R., Monsell, S., Sahakian, B. J., & Robbins, B. W. (2004). A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. *Brain*, *127*, 1561-1573.
- Baranek, G. T., Danko, C. D., Skinner, M. L., Bailey, D. B., Hatton, D. D., Roberts, J. E. et al. (2005). Video analysis of sensory-motor features in infants with fragile X syndrome at 9-12 months of age. *Journal of Autism and Developmental Disorders*, *35*, 645-656.
- Belser, R. C. & Sudhalter, V. (2001). Conversational characteristics of children with fragile X syndrome: Repetitive speech. *American Journal on Mental Retardation*, *106*, 28-38.
- Bertella, L., Girelli, L., Grugni, G., Marchi, S., Molinari, E. & Carlo, S. (2005). Mathematical skills in Prader-Willi Syndrome. *Journal of Intellectual Disability Research*, *49*, 159-169.
- Bodfish, J. (2004). Phenomenology of repetitive behaviour in autism: Comparison to non-specific intellectual disability. *Journal of Intellectual Disability Research*, *48*, 292-292.
- Bodfish, J. W., Symons, F. J., Parker, D. E. & Lewis, M. H. (2000). Varieties of repetitive behaviour in Autism: Comparison to Mental Retardation. *Journal of Autism and Developmental Disorders*, *30*, 237-243.
- Boer, H, Holland, A. J, Whittington, J. E, Butler, J., Webb, T. & Clarke, D. (2002). Psychotic illness in people with Prader-Willi syndrome due to chromosome 15 maternal uniparental disomy. *The Lancet*, *359*, 135-136.
- Braddick, O., Atkinson, J. & Wattam-Bell, J. (2003). Normal and anomalous development of visual motion processing: motion coherence and 'dorsal-stream vulnerability'. *Neuropsychologia*, *41*, 1769-1784.
- Chang, S. W. (2006). Methods in scaling the basic competence test. *Educational and Psychological Measurement*, *66*, 907-929.

- Clarke, D. J., Boer, H., Whittington, J., Holland, A., Butler, J. & Webb, T. (2002). Prader-Willi syndrome, compulsive and ritualistic behaviours: The first population-based survey. *British Journal of Psychiatry*, *180*, 358-362.
- Cornish, K. M., Munir, F. & Cross, G. (2001). Differential Impact of the FMR-1 Full Mutation on Memory and Attention Functioning: A Neuropsychological Perspective. *Journal of Cognitive Neuroscience*, *13*, 144-150.
- Cornish, K. M., Sudhalter, V. & Turk, J. (2004). Attention and language in Fragile-X syndrome. *Mental Retardation and Developmental Disabilities*, *10*, 11-16.
- Cornish, K., Swainson, R., Cunnington, R., Wilding, J., Morris, P. & Jackson, G. (2004). Do women with fragile X syndrome have problems in switching attention: Preliminary findings from ERP and fMRI. *Brain and Cognition*, *54*, 235-239.
- Cullen, B., Coen, R. F., Lynch, C. A., Cunningham, C. J., Coakley, D. & Robertson, I. H. (2005). Repetitive behaviour in Alzheimer's disease: Description, correlates and functions *International Journal of Geriatric Psychiatry*, *20*, 686-693.
- Derfuss, J., Brass, M., Neumann, J., & von Cramon, D. Y. (2005). Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. *Human Brain Mapping*, *25*, 22-34.
- Dias, R., Robbins, T. W., & Roberts, A. C. (1996). Primate analogue of the Wisconsin Card Sorting Test: Effects of excitotoxic lesions of the prefrontal cortex in the marmoset. *Behavioural Neuroscience*, *110*, 872-886.
- Dykens, E. M. (2004). Maladaptive and compulsive behavior in Prader-Willi syndrome: New insights from older adults. *American Journal on Mental Retardation*, *109*, 142-153.
- Dykens, E. M. (2002). Are jigsaw puzzle skills "spared" in persons with Prader-Willi syndrome? *Journal of Child Psychology and Psychiatry*, *43*, 343-352.
- Evans, D. W. & Gray, F. L. (2000). Compulsive-like behaviour in individuals with Down syndrome: Its relation to mental age level, adaptive and maladaptive behaviour. *Child Development*, *71*, 288-300.
- Evans, D. W., Leckman, J. F., Carter, A., Reznick, J. S., Henshaw, D. & King, R. A. (1997). Ritual, Habit and Perfectionism: The Prevalence and Development of Compulsive-like Behaviour in Normal Young Children. *Child Development*, *68*, 1, 58-68.
- Feinstein, C. & Reiss, A.L. (1998). Autism: The Point of View from Fragile-X Studies. *Journal of Autism and Developmental Disorders*, *28*, 393-403.
- Forstmann, B. U., Brass, M., Koch, I., & von Cramon, D. Y. (2005). Internally generated and directly cued task sets: an investigation with fMRI. *Neuropsychologia*, *43*, 943-952.

- Greaves, N., Prince, E., Evans, D. W., & Charman, T. (2006). Repetitive and ritualistic behaviour in children with Prader-Willi syndrome and children with autism. *Journal of Intellectual Disability Research*, *50*, 92-100.
- Hessl, D., Glaser, B., Dyer-Friedman, J., Blasey, C., Hastie, T. & Gunnar, M. (2002). Cortisol and behaviour in Fragile-X syndrome. *Psychoneuroendocrinology*, *27*, 855-872.
- Holland, A. J., Whittington, J. E., Butler, J., Webb, T., Boer, H. & Clarke, D. (2003). Behavioural phenotypes associated with specific genetic disorders: Evidence from a population-based study of people with Prader-Willi syndrome. *Psychological Medicine*, *33*, 141-153.
- Iwata, B. A., Dorsey, M. F., Slifer, K. J., Bauman, K. E., & Richman, G. S. (1994). Toward a functional analysis of self-injury. *Journal of Applied Behavior Analysis*, *27*, 197-209.
- Jauregi, J., Arias, C., Vegas, O., Alén, F., & Martinez, S., Copet, P. et al. (2007) A neuropsychological assessment of frontal cognitive functions in Prader-Willi syndrome. *Journal of Intellectual Disability Research*, *51*, 350-365.
- Jurado, M. B. & Rosselli, M. (2007). The elusive nature of executive functions: A review of our current understanding. *Neuropsychology Review*, *17*, 213-233.
- Klingberg, T. Forssberg, H. & Westerberg, H. (2002). Training of working memory in children with ADHD. *Journal of Clinical and Experimental Neuropsychology*, *24*, 781-791.
- Kogan, C. S., Boutet, I., Cornish, K., Zangenehpour, S., Mullen, K. T., Holden, J. J. A. et al. (2004). Differential impact of the FMR1 gene on visual processing in fragile X syndrome. *Brain*, *127*, 591-601.
- Loesch, D. Z, Huggins, R. M, & Hagermann, R. J. (2004). Phenotypic variation and FMRP levels in Fragile-X Syndrome. *Mental Retardation and Developmental Disabilities* *10*, 31-41.
- Lopez, B. R., Lincoln, A. J., Ozonoff, S. & Lai, Z. (2005). Examining the relationship between executive functions and restricted, repetitive symptoms of autistic disorder. *Journal of Autism and Developmental Disorders* *35*, 445-460.
- Manly, T., Anderson, V., Nimmo-Smith, I., Turner, A., Watson, P. & Robertson, I. H. (2005). The differential assessment of children's attention: The Test of Everyday Attention for Children (TEA-Ch), normative sample and ADHD performance. *Journal of Child Psychology and Psychiatry*, *42*, 1065-1081.
- Manly, T., Robertson, I.H., Anderson, V. & Nimmo-Smith, I. (1999). *The Test of Every Day Attention for Children*, Harcourt Assessment UK, London.
- Mason, D.J., Humphreys, G.W. & Kent, L.S. (2003). Exploring selective attention in ADHD: visual search through space and time. *Journal of Child Psychology and Psychiatry*, *44*, 1158-1176.

- Milner, K. M., Craig, E. E., Thompson, R. J., Veltman, M. W., Thomas, N. S., Roberts, S. et al. (2005). Prader-Willi syndrome: intellectual abilities and behavioural features by genetic subtype. *Journal of Child Psychology and Psychiatry*, *46*, 1089-1096.
- Moss, J. & Oliver, C. (2008). *The Repetitive Behaviour Questionnaire. Manual for administration and scorer interpretation*. University of Birmingham, UK..
- Moss, J., Oliver, C., Arron, K., Burbidge, C. & Berg, K. (in press). The Prevalence and Phenomenology of Repetitive Behaviour in Genetic Syndromes. *Journal of Autism and Developmental Disorders*.
- Munir, F., Cornish, K. M. & Wilding, J. (2000) A neuropsychological profile of attention deficits in young males with fragile X syndrome. *Neuropsychologia* *38*, 1261-1270.
- Pietrefesa, A. S. & Evans, D. W. (2007). Affective and neuropsychological correlates of children's rituals and compulsive-like behaviors: Continuities and discontinuities with obsessive-compulsive disorder. *Brain and Cognition*, *65*, 36-46.
- Riddle, J. E., Cheema, A., Sobesky, W. E., Gardner, S. C., Taylor, A. K., Pennington, B. F. et al. (1998). Phenotypic involvement in females with the FMR1 Gene mutation. *American Journal on Mental Retardation*, *102*, 590-601.
- Rogers, R. D., & Monsell, S. (1995). Costs of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology*, *124*, 207-231.
- Ruge, H., Brass, M., Koch, I., Rubin, O., Meiran, N. & von Cramon, D. Y. (2005). Advance preparation and stimulus-induced interference in cued task switching: further insights from BOLD fMRI. *Neuropsychologia*, *43*, 340-355.
- Rushworth, M. F. S., Hadland, K. A., Gaffan, D., & Passingham, R. E. (2003). The effect of cingulate cortex lesions on task switching and working memory. *Journal of Cognitive Neuroscience*, *15*, 338-353.
- Schumacher, E. H., Cole, M. W., & D'Esposito, M. (2007). Selection and maintenance of stimulus-response rules during preparation and performance of a spatial choice-reaction task. *Brain Research*, *1136*, 77-87.
- Simon, J. R. (1969). Reactions towards the source of stimulation. *Journal of Experimental Psychology*, *81*, 174-176.
- Siomi, H., Siomi, M. C., Nussbaum, R. L., & Dreyfuss, G. (1993). The Protein Product of the Fragile-X Gene, FMR1, Has Characteristics of An RNA-Binding Protein. *Cell*, *74*, 291-298.
- Smith, E. E. & Jonides, J. (1999). Storage and executive processes in frontal lobes. *Science*, *283*, 1658-1661.

- Stauder, J. E. A., Boer, H., Gerits, R. H. A., Tummers, A., Whittington, J. & Curfs, L. M. G. (2005). Differences in behavioural phenotype between parental deletion and maternal uniparental disomy in Prader-Willi syndrome: an ERP study. *Clinical Neurophysiology*, *116*, 1464-1470.
- Stauder, J.E.A., Brinkman, M.J.R. & Curfs, L.M.G. (2002). Multi-modal P3 deflation of event-related brain activity in Prader-Willi syndrome. *Neuroscience Letters*, *327*, 99-102.
- Steinhausen, H.C., von Gontard, A., Spohr, H.L., Hauffa, B.P., Eiholzer, U. & Backes, M. (2002). Behavioural phenotypes in four mental retardation syndromes: Foetal Alcohol Syndrome, Prader-Willi syndrome, Fragile-X syndrome and Tuberous Sclerosis. *American Journal of Medical Genetics*, *111*, 381-387.
- Symons, F. J., Clark, R. D., Hatton, D. D., Skinner, M., & Bailey, D. B. (2003). Self-injurious behaviour in young boys with fragile X syndrome. *American Journal of Medical Genetics Part A*, *118A*, 115-121.
- Turner, M.A. (1999). Generating novel ideas: Fluency performance in high functioning and Learning Disabled individuals with Autism. *Journal of Child Psychology and Psychiatry*, *40*, 189-201.
- Turner, G., Webb, T., Wake, S., & Robinson, H. (1996). Prevalence of Fragile-X syndrome. *American Journal of Medical Genetics*, *64*, 196-197.
- Walley, R. M. & Donaldson, M. D. C. (2005). An investigation of executive function abilities in adults with Prader-Willi syndrome. *Journal of Intellectual Disability Research*, *49*, 613-625.
- Wechsler, D., Golombok, S. & Rust, J. (1992). *Wechsler Intelligence Scales for Children-Third Edition UK*. Psychology Corporation, UK.
- Whittington, J., Holland, A., Webb, T., Butler, J., Clarke, D. & Boer, H. (2004 a). Cognitive abilities and genotype in a population-based sample of people with Prader-Willi syndrome. *Journal of Intellectual Disability Research*, *48*, 172-187.
- Whittington, J., Holland, A., Webb, T., Butler, J., Clarke, D. & Boer, H. (2004b). Academic underachievement by people with Prader-Willi syndrome. *Journal of Intellectual Disability Research*, *48*, 188-200.
- Whittington, J. E, Holland, A. J, Webb, T, Butler, J., Clarke, D. & Boer, H. (2001). Population prevalence and estimated birth incidence and mortality rate for people with Prader-Willi syndrome in one UK Health Region. *Journal of medical genetics*, *38*, 792-798.
- Wigren, M. & Hansen, S. (2005). ADHD symptoms and insistence on sameness in Prader-Willi syndrome. *Journal of Intellectual Disability Research*, *49*, 449-456.
- Wigren, M. & Hansen, S. (2003). Rituals and compulsivity in Prader-Willi syndrome: Profile and stability. *Journal of Intellectual Disability Research*, *47*, 428-438.

- Wigren, M. & Heimann, M. (2001). Excessive picking in Prader-Willi syndrome: A pilot study of phenomenological aspects and comorbid symptoms. *International Journal of Disability, Development and Education*, 48, 129-142.
- Wilding, J., Cornish, K., & Munir, F. (2002). Further delineation of the executive deficit in males with fragile-X syndrome. *Neuropsychologia*, 40, 1343-1349.
- Woodcock, K. A., Humphreys, G. W. & Oliver, C. (in press). Dorsal and ventral stream mediated visual processing in genetic subtypes of Prader-Willi syndrome. *Neuropsychologia*.
- Woodcock, K. A., Oliver, C. & Humphreys, G. W. (in press). Associations between repetitive questioning, resistance to change, temper outbursts and anxiety in Prader-Willi and Fragile-X syndromes. *Journal of Intellectual Disability Research*.
- Woodward, T. S., Ruff, C. C., & Ngan, E. T. C. (2006). Short- and long-term changes in anterior cingulate activation during resolution of task-set competition. *Brain Research*, 1068, 161-169.

Table 1. Shows means and standard deviations of scores on each of the dependent measures obtained from the TEACH. F-statistics and p-values are given for the interactions between group and TEACH dependent variables in two multivariate ANCOVAs: individual dependent variables from the TEACH compose separate between subject factors, while i) PWS and TD groups, and ii) FraX and TD groups, compose separate levels on the fixed group factor. Interactions significant to a corrected level of $p < .01$ are presented in shaded cells.

TEACH Dependent Variable	PWS	FraX	TD	PWS, TD	FraX, TD
	Mean (SD)	Mean (SD)	Mean (SD)	$F(1,51)$	$F(1,40)$
Sky Search Number of targets (more targets → greater ability)	15.70 (4.75)	8.05 (3.97)	18.57 (2.64)	4.43 $p = .040$	3.79 $p = .059$
Sky Search Time per target (s) (shorter time → greater ability)	11.56 (4.88)	14.74 (11.23)	6.46 (2.16)	7.15 $p = .010$	3.55 $p = .067$
Sky Search Attention score (lower score → greater ability)	9.12 (4.43)	12.36 (9.95)	4.95 (1.93)	8.17 $p = .006$	3.20 $p = .081$
Sky Search Dual task decrement (lower score → greater ability)	84.04 (118.94)	109.72 (222.46)	3.48 (4.77)	12.25 $p = .001$	5.14 $p = .029$
Walk Don't Walk Number correct (more correct → greater ability)	7.53 (4.20)	5.26 (4.33)	13.00 (3.03)	6.17 $p = .017$	12.01 $p = .001$
Opposite Worlds Same world time (s) (shorter time → greater ability)	39.38 (15.00)	79.30 (39.09)	25.69 (6.78)	5.61 $p = .022$	12.09 $p = .001$
Opposite Worlds Opposite world time (s) (shorter time → greater ability)	57.70 (23.43)	104.79 (48.58)	34.60 (12.62)	2.86 $p = .097$	15.64 $p < .001$
Opposite Worlds Opposite world time (s) minus same world time (s) (shorter time → greater ability)	18.32 (15.79)	25.49 (34.93)	8.91 (7.50)	0.16 $p = .688$	1.51 $p = .226$

Table 2. Shows the mean and standard deviation of reaction times in milliseconds and the proportion of accurate responses to trials in single task and mixed task blocks of the Simon task across PWS, FraX and TD groups. Congruent, non-congruent, switch and no-switch trial types are reported separately.

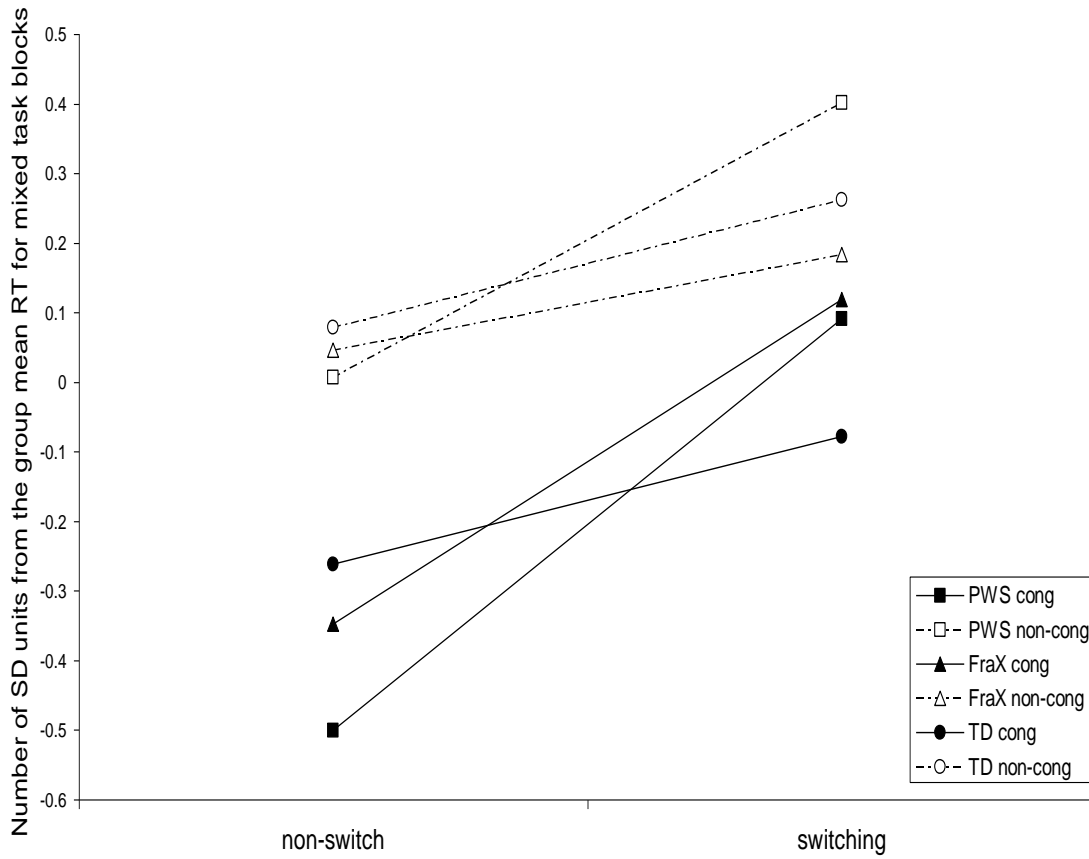
Block	Task	Congruency	Switching	PWS	FraX	TD
				Mean RT(ms) (SD)		
% accurate responses						
Single Task Blocks	Identity	Congruent		1087.83 (366.98) 0.98	1607.26 (1026.07) 0.93	732.51 (251.14) 0.93
		Non-congruent		1216.51 (447.57) 0.96	1788.97 (1235.58) 0.90	735.93 (200.84) 0.91
	Location	Congruent		1175.32 (448.90) 0.97	2320.87 (2224.38) 0.88	577.70 (209.63) 0.99
		Non-congruent		1384.11 (628.52) 0.83	3106.63 (3789.00) 0.47	591.13 (239.29) 0.98
Mixed Task Blocks	Identity	Congruent	Switch	1525.15 (992.42) 0.99	2895.11 (3315.17) 0.92	883.14 (555.80) 0.99
			No-switch	1136.09 (473.53) 0.96	1595.65 (1022.66) 0.86	838.55 (542.21) 0.96
		Non-congruent	Switch	1639.61 (790.36) 0.83	2810.36 (2196.97) 0.78	1123.78 (961.17) 0.86
			No-switch	1570.19 (924.04) 0.86	1811.04 (958.15) 0.87	1053.81 (903.09) 0.89
	Location	Congruent	Switch	1587.72 (941.15) 1.00	2142.29 (1441.79) 0.94	662.72 (258.55) 1.00
			No-switch	1230.06 (523.01) 0.99	1948.17 (1249.77) 0.88	560.29 (195.74) 0.98
		Non-congruent	Switch	1864.99 (1366.66) 0.54	2435.02 (2496.33) 0.30	694.63 (293.80) 0.94
			No-switch	1436.36 (650.11) 0.67	2993.92 (3287.10) 0.29	617.96 (259.14) 0.98

Table 3. Shows the means and standard deviations of scores on items of the RBQ and CRI for the PWS, FraX and TD groups. *F*-statistic and *p*-values are shown for the interactions between group and each RBQ/ CRI item factor in the multivariate ANCOVAs considering i)PWS and TD groups, and ii) FraX and TD groups. Only items on which there was at least one significant group difference are shown⁵; items associated with no significant group interactions are shown in Appendix C.

		PWS Mean (SD)	FraX Mean (SD)	TD Mean (SD)	PWS vs. TD		FraX vs. TD	
					<i>F</i> (1,52)	<i>p</i>	<i>F</i> (1,52)	<i>p</i>
R	Repetitive Questions	3.50 (0.84)	3.00 (1.47)	0.46 (0.96)	41.04	<0.001	9.98	<0.01
B								
Q	Preference for routine	3.29 (1.33)	2.39 (1.73)	0.36 (0.95)	47.78	<0.001	6.85	0.01
	Lining up & arranging objects	0.79 (1.45)	1.07 (1.63)	0.43 (0.84)	0.01	0.91	12.02	0.001
	Just right behaviour	1.57 (1.75)	1.36 (1.75)	0.14 (0.36)	6.42	0.01	1.78	0.19
	Completing behaviour	1.86 (1.69)	0.68 (1.28)	0.14 (0.45)	6.72	0.01	3.14	0.08
C	Preference for a particular order	3.71 (1.58)	3.11 (1.55)	1.64 (0.95)	31.03	<0.001	14.73	<0.001
R								
I	/certain way.							
	Arrange objects/ perform behaviours until “just right”	2.21 (1.47)	1.82 (1.31)	1.46 (0.92)	6.61	0.01	5.77	0.02
	Persistent habits?	4.14 (1.27)	3.61 (1.57)	2.07 (1.36)	9.91	<0.01	3.91	0.05
	Line up / arrange objects	1.82 (1.44)	2.00 (1.59)	1.54 (1.00)	0.02	0.88	8.56	<0.01
	Prefer same routine.	4.32 (1.33)	3.82 (1.61)	1.75 (1.24)	28.03	<0.001	9.81	<0.001
	Act out same thing over & over.	3.21 (1.75)	3.14 (1.67)	1.21 (0.69)	20.60	<0.001	9.35	<0.001
	Insists on belongings being in their place.	2.54 (1.62)	2.82 (1.79)	1.25 (0.59)	6.77	0.01	4.04	0.05
	Repetitive actions.	2.79 (1.73)	3.25 (1.58)	1.11 (0.42)	5.16	0.03	9.36	<0.001
	Eats food in a particular way.	2.93 (1.90)	2.32 (1.85)	1.50 (1.17)	9.63	<0.01	0.56	0.46
	Bedtime routine.	3.25 (1.94)	3.32 (1.93)	2.54 (1.84)	7.73	0.01	1.64	0.21

⁵Interactions with group that were significant to $p \leq .01$ are presented in shaded cells.

Figure 1. Compares the effect of congruency and switching in mixed task blocks of the Simon task, in the PWS, FraX and TD groups. RTs are plotted as the distance (in standard deviation units) between the mean RT across all mixed block trials (each group separately) and the mean RT for each of the four types of trial (switch congruent, switch non-congruent, non-switch congruent, non-switch non-congruent).



APPENDIX A

Table A1. Shows the mean and standard deviations of the raw scores of PWS, FraX and TD groups on the WISC subtests. Independent samples t-tests compared raw scores between the groups and showed significant differences between all groups on all subtests; these *t*- and *p*- values are also shown.

	Similarities	Vocabulary	Block Design	Object Assembly
PWS	9.43 (4.40)	17.14 (7.13)	16.60 (11.61)	15.00 (7.53)
FraX	6.42 (2.91)	10.29 (3.60)	4.43 (4.02)	10.65 (6.18)
TD	16.32 (5.90)	28.46 (9.84)	34.46 (14.89)	24.20 (7.37)
PWS vs. TD	<i>t</i> (54)= 4.96, <i>p</i> < .001	<i>t</i> (54)= 4.93, <i>p</i> < .001	<i>t</i> (54)= 5.00, <i>p</i> < .001	<i>t</i> (54)= 4.62, <i>p</i> < .001
PWS vs. FraX	<i>t</i> (45)=2.82, <i>p</i> = .007	<i>t</i> (54)= 4.55, <i>p</i> < .001	<i>t</i> (47)= 5.15, <i>p</i> < .001	<i>t</i> (46)= 2.12, <i>p</i> = .039

APPENDIX B

Table B1. Shows the standardised RTs for single task and mixed task blocks of the Simon task considering PWS, FraX and TD groups in turn. Congruent, non-congruent, switch and no-switch trial types are reported separately.

Block	Task	Congruency	Switch	PWS	FraX	TD
				Standard RT & calculation		
Single Task Blocks	Identity	Congruent		-0.29 (1087.83 -1215.94) /438.81	-0.35 (1607.26 -2205.93) /1718.84	0.35 (732.51 -659.32) /209.36
		Non-congruent		0.00 (1216.51 -1215.94) /438.81	-0.24 (1788.97 -205.93) /1718.84	0.37 (735.93 -659.32) /209.36
	Location	Congruent		-0.09 (1175.32 -1215.94) /438.81	0.07 (2320.87 -2205.93) /1718.84	-0.39 (577.70 -659.32) /209.36
		Non-congruent		0.38 (1384.11 -1215.94) /438.81	0.52 (3106.63 -2205.93) /1718.84	-0.33 (591.13 -659.32) /209.36
Mixed Task Blocks	Identity	Congruent	Switch	0.04 (1525.15 -1498.77) / 631.24	0.35 (2895.11 -2328.95) /1601.15	0.20 (883.14 -804.36) /400.33
			No-switch	-0.57 (1136.09 -1498.77) / 631.24	-0.46 (1595.65 -2328.95) /1601.15	0.09 (838.55 -804.36) /400.33
	Non-congruent	Switch	0.22 (1639.61 -1498.77) / 631.24	0.30 (2810.36 -2328.95) /1601.15	0.80 (1123.78 -804.36) /400.33	
		No-switch	0.11 (1570.19 -1498.77) / 631.24	-0.32 (1811.04 -2328.95) /1601.15	0.62 (1053.81 -804.36) /400.33	
	Location	Congruent	Switch	0.14 (1587.72 -1498.77) / 631.24	-0.12 (2142.29 -2328.95) /1601.15	-0.35 (662.72 -804.36) /400.33
			No-switch	-0.43 (1230.06 -1498.77) / 631.24	-0.24 (1948.17 -2328.95) /1601.15	-0.61 (560.29 -804.36) /400.33
		Non-congruent	Switch	0.58 (1864.99 -1498.77) / 631.24	0.07 (2435.02 -2328.95) /1601.15	-0.27 (694.63 -804.36) /400.33
			No-switch	-0.10 (1436.36 -1498.77) / 631.24	0.42 (2993.92 -2328.95) /1601.15	-0.47 (617.96 -804.36) /400.33

APPENDIX C

Table C1. Shows the means and standard deviations of scores on items of the RBQ for the PWS, FraX and TD groups. F-statistic and p-values are shown for the interactions between group and each RBQ item factor in the two multivariate ANCOVAs considering i)PWS and TD groups, and ii) FraX and TD groups. Only those items are shown here that were associated with no significant interactions with group.

RBQ Item	PWS Mean (SD)	FraX Mean (SD)	TD Mean (SD)	PWS vs. TD		FraX vs. TD	
				F (1,52)	p	F (1,52)	p
Object Stereotypy	1.18 (1.72)	1.57 (1.89)	0.75 (1.32)	3.64	0.06	0.78	0.38
Body Stereotypy	1.07 (1.49)	2.00 (1.94)	1.00 (1.49)	<0.001	0.98	<0.001	>0.99
Hand Stereotypy	1.89 (1.83)	2.86 (1.56)	0.43 (1.26)	3.08	0.09	2.48	0.12
Cleaning	0.86 (1.46)	0.82 (1.61)	0.54 (1.23)	0.27	0.61	0.12	0.73
Tidying Up	0.64 (1.19)	1.29 (1.80)	0.14 (0.45)	0.00	0.96	0.01	0.91
Hoarding	2.00 (1.72)	1.36 (1.70)	0.61 (0.96)	1.93	0.17	4.18	0.05
Organising Objects	0.71 (1.15)	0.96 (1.62)	0.29 (0.76)	3.48	0.07	6.12	0.02
Attachment to particular people	1.75 (1.46)	1.96 (1.75)	0.57 (1.00)	0.21	0.65	0.00	0.96
Attachment to Objects	1.21 (1.69)	1.54 (1.82)	0.43 (1.10)	5.03	0.03	1.93	0.17
Repetitive Phrases / Signing	1.18 (1.66)	2.57 (1.85)	0.29 (0.81)	1.91	0.17	5.68	0.02
Rituals	0.50 (1.20)	1.14 (1.78)	0.25 (0.70)	0.08	0.78	2.53	0.12
Restricted Conversation	2.00 (1.59)	2.50 (1.60)	0.36 (0.87)	6.35	0.02	4.88	0.03
Echolalia	1.43 (1.79)	2.75 (1.55)	0.46 (1.00)	0.90	0.35	0.50	0.48
Spotless behaviour	1.00 (1.59)	0.71 (1.46)	0.18 (0.55)	0.47	0.50	0.37	0.54

Table C2. Shows the means and standard deviations of scores on items of the CRI for the PWS, FraX and TD groups. *F*-statistic and *p*-values are shown for the interactions between group and each CRI item factor in the two multivariate ANCOVAs considering i) PWS and TD groups, and ii) FraX and TD groups. Only those items are shown here that were associated with no significant interactions with group.

CRI Item	PWS Mean (SD)	FraX Mean (SD)	TD Mean (SD)	PWS vs. TD		FraX vs. TD	
				<i>F</i> (<i>df</i>)	<i>p</i>	<i>F</i> (<i>df</i>)	<i>p</i>
Attachment to objects.	2.29 (1.72)	2.96 (1.84)	2.00 (1.59)	0.88	0.35	5.97	0.02
Concern with dirt, cleanliness / neatness.	2.11 (1.62)	2.36 (1.59)	1.46 (1.10)	0.35	0.56	0.82	0.37
Strong preferences for certain foods.	2.07 (1.65)	3.29 (1.90)	2.21 (1.50)	0.23	0.63	0.81	0.37
Sensitive to how clothes feel.	3.11 (1.81)	3.18 (1.87)	2.25 (1.46)	1.28	0.26	0.31	0.58
Preference for wearing certain articles of clothing.	2.61 (1.75)	3.04 (1.93)	2.18 (1.54)	2.20	0.14	1.33	0.25
Collect / store objects.	3.25 (1.69)	2.11 (1.52)	2.11 (1.26)	6.14	0.02	0.44	0.51
Aware of details.	1.82 (1.39)	2.75 (1.78)	1.21 (0.69)	0.03	0.86	2.07	0.16
Prefer to stick to one activity rather than change to a new one.	2.29 (1.61)	2.89 (1.81)	1.39 (0.79)	3.77	0.06	0.43	0.51
Requests to postpone going to bed.	2.71 (1.70)	2.75 (1.69)	2.71 (1.58)	1.47	0.23	0.69	0.41

APPENDIX D

Table D1. Shows Pearson's correlation coefficients and associated *p*-values for correlations between standard scores for switch cost and scores for items on the RBQ and CRI across participants in PWS, FraX and TD groups. Correlations significant to $p \leq .05$ are shaded in dark grey.

RBQ Item	Pearson's <i>r</i> (<i>df</i> =80)	<i>P</i>	CRI Item	Pearson's <i>r</i> (<i>df</i> =80)	<i>p</i>
Object Stereotypy	.126	.259	Preference for a particular order /certain way.	.218	.050
Body Stereotypy	.143	.199	Attachment to objects.	.081	.417
Hand Stereotypy	.290	.008	Concern with dirt, cleanliness / neatness.	.175	.117
Cleaning	-.112	.315	Arrange objects/ perform behaviours until "just right"	.154	.167
Tidying Up	-.158	.156	Persistent habits?	.158	.155
Hoarding	.094	.400	Line up / arrange objects	.115	.302
Organising Objects	< .001	.998	Prefer same routine.	.272	.014
Attachment to particular people	.115	.304	Act out same thing over & over.	.184	.098
Repetitive Questions	.188	.090	Insists on belongings being in their place.	.075	.506
Attachment to Objects	.097	.388	Repetitive actions.	.097	.384
Repetitive Phrases / Signing	.031	.780	Strong preferences for certain foods.	-.174	.118
Rituals	.111	.322	Eats food in a particular way.	-.042	.708
Restricted Conversation	-.037	.742	Sensitive to how clothes feel.	-.135	.226
Echolalia	.208	.060	Preference for wearing certain articles of clothing.	-.029	.795
Preference for routine	.310	.005	Collect / store objects.	-.071	.529
Lining up & arranging objects	.108	.335	Aware of details.	.215	.052
Just right behaviour	.089	.428	Prefer to stick to one activity rather than change to a new one.	.089	.428
Completing behaviour	.229	.038	Requests to postpone going to bed.	-.101	.365
Spotless behaviour	.109	.331	Bedtime routine.	.209	.060