Dorsal and ventral stream mediated visual processing in genetic subtypes of Prader-Willi syndrome

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Abstract

Previous work has suggested that there are specific deficits in dorsal stream processing in a variety of developmental disorders. Prader-Willi syndrome (PWS) is associated with two main genetic subtypes; deletion and disomy. Relative strengths in visual processing are shown in PWS, although these strengths may be specific to the deletion subtype. We investigated visual processing in PWS using an adapted Simon task which contrasted location (dorsal stream) and shape identity (ventral stream) tasks. Compared to a group of typically developing children, children with PWS deletion showed a greater degree of impairment in the dorsal stream task than in the ventral stream task, a pattern similar to that shown in a group of boys with Fragile-X syndrome. When matched on a measure of non-verbal ability, children with PWS disomy showed the opposite pattern with better performance in the location compared to the shape task, although these task performance asymmetries may have been linked to executive control processes. It is proposed that children with PWS deletion show a relative strength in visual processing in the ventral stream along with a specific deficit in dorsal stream processing. In contrast, children with PWS disomy show neither effect.

Keywords:
Fragile-X syndrome
Paternal deletion
Uniparental disomy
Dorsal stream deficit
Dorsal stream vulnerability
Chromosome 15

Introduction

In 1982 Mishkin and Ungerleider carried out a series of lesion studies with monkeys demonstrating that pattern discrimination functions of the inferior temporal cortex and visuo-spatial functions of the parietal pre-occipital cortex were critically dependent on projections from different groups of neurons in the striate cortex. Following this research, two similarly distinct visual processing pathways have been described in humans. These comprise a ventral stream responsible for processing the surface characteristics of stimuli and a dorsal stream responsible for processing position information for action. (E.g. Bruno, Bernardis & Gentilucci, 2008; Ganel & Goodale, 2003; Milner & Goodale, 2008; although see Pisella, Binkofski, Lasek, Toni & Rossetti, 2006; Rossetti, Pisella & Vighetto, 2003, for alternative views). The distinction between ventral and dorsal visual processing has been influential for researchers investigating abnormal development of visual processing in various disorders.

Atkinson et al. (1997) tested visual functioning in children with Williams syndrome which is a genetic disorder associated with a deletion on chromosome 7. Performance on motion coherence and post box posting tasks (measures of dorsal stream functioning) was compared with that on form coherence and post box slot orienting tasks (orienting a slot to align with the slot in a post-box; measures of ventral stream functioning). Children with Williams syndrome were relatively more impaired in the tests of dorsal stream functioning than in the tests of ventral stream functioning when compared to typically developing children. This has been supported using diffusion tensor imaging (Hoeft et al., 2007), when measures of diffusivity in brain regions

associated with dorsal and ventral streams (superior verses inferior longitudinal fasciculus) were compared between children with Williams syndrome and typically developing or intellectual disabled controls. The results suggested a greater degree of neuronal abnormality in individuals with Williams syndrome compared to controls, particularly in brain regions associated with dorsal stream visual processing.

Using similar comparisons of form and motion coherence thresholds, a specific deficit in dorsal versus ventral stream processing has also been demonstrated in children with autism (Spencer et al., 2000) and individuals with developmental dyslexia (Hansen, Stein, Orde, Winter & Talcott, 2002). This has led to the proposal that the dorsal stream may be particularly vulnerable to impairment; a suggestion supported by studies of the development of visual processing in young children (Braddick, Atkinson, Wattam-Bell, 2003). However, O'Brien, Spencer, Atkinson, Braddick & Wattam-Bell (2002) found that individuals with developmental dyspraxia showed a specific deficit in ventral stream processing compared to individuals matched for age and verbal IQ, but no corresponding deficit in dorsal stream processing. This suggests that both dorsal and ventral streams can be selectively impaired in different developmental disorders.

Fragile-X syndrome (FraX), an X-linked genetic disorder associated with a single gene mutation and subsequent failure of FMR-1 protein transcription (Fu, Kuhl & Pizzuti, 1991; Siomi, Siomi & Nussbaum, 1993) is another disorder associated with a specific deficit in dorsal relative to ventral stream processing (Kogan et al., 2004). Kogan et al. showed that the histological structure of the lateral geniculate nucleus was abnormal in males with FraX. This abnormality predominantly affected the

neurons projecting to the dorsal stream (magnocellular neurons) and was due to the absence of the normally high levels of FMR-1 expression in these neurons. It was therefore suggested that differences in FMR-1 expression across different developmental disorders might be associated with the dorsal stream deficits.

In this paper we investigate dorsal and ventral stream visual processing in another developmental disorder, Prader-Willi syndrome (PWS: 1: 10,000 to 1:25,000 live births), which is associated with learning disability. There are two main genetic subtypes of PWS, a paternal deletion of chromosome 15q11-q13 (60-70%) and maternal uniparental disomy (UPD) of chromosome 15 (25-30%: Whittington et al., 2001). Individuals with PWS show specific deficits in various areas of cognitive functioning, including auditory processing, mathematical skills and short-term memory (Bertella et al., 2005; Stauder, Brinkman & Curfs, 2002; Walley & Donaldson, 2005). Importantly however, performance on psychometric tests and good performance on jigsaw puzzles has suggested relative strengths in visual processing in individuals with the deletion subtype of PWS, although not in individuals with the UPD subtype (Fox, Yand, Feurer, Butler & Thompson, 2001; Dykens, 2002). It is unknown whether the apparent strength in visual processing in deletion PWS individuals is restricted to either the dorsal or ventral processing stream, or extends to both. The nature of the difference in visual processing between deletion and UPD PWS individuals is also unknown.

We report the performance of PWS individuals along with that of boys with Fragile X syndrome and typically developing individuals on tasks requiring responses either to the identities of shapes or to the locations of the shapes. Previously these tasks have

been used to assess the effects of response conflict, which typically arise in the shape identification version when the stimuli fall in locations that are incongruent with the required manual (left-right) responses (Simon, 1969; Stürmer, Siggelkow, Dengler, & Leuthold, 2000). The asymmetrical interference on incongruent trials (greater interference for the shape relative to the location task), has been taken as evidence for the dominance of the location task when spatially-coded manual responses are made (Melera et al., 2008). However, irrespective of the differential interference effects that arise, the properties of the stimuli that must be processed for each task conform to attributes for which the dorsal and ventral visual routes are specialised (location and shape judgements). This is confirmed by studies using functional brain imaging. Tasks requiring selection of the spatial locations of visual elements show activation in a network of dorsal parietal and frontal brain regions (including the precuneus and superior parietal lobe; Schumacher, Cole & D'Esposito, 2007; Schumacher, Elston & D'Esposito, 2003), while shape identification performance in the tasks is associated with activation of the fusiform gyrus (Withforth et al., 2006). Hence the contrast between location judgements, on the one hand, and shape identity judgements on the other, can be linked to differential processing within the dorsal and ventral streams, irrespective of variations in more executive aspects of the tasks (arising when the irrelevant dimensions of the stimulus is incongruent with the required response). Aspects of executive functioning in the tasks, in the participants examined here, are reported in detail in Woodcock, Oliver and Humphreys (sub., a, b).

Here we first report data on the location and shape identity tasks generated by a group of children with the deletion subtype of PWS in comparison to data from a younger group of typically developing children (selected to be at a similar level of intellectual

functioning), and to a group of boys with FraX (known to be associated with impairment in dorsal stream processing). We then compare children with the UPD subtype of PWS to two deletion PWS groups, one matched for verbal IQ and the other for non-verbal IQ. We included two PWS deletion groups because when comparing the two subtypes, higher non-verbal IQ has been reported in individuals with a deletion, with higher verbal IQ in individuals with UPD (Roof et al., 2000). We ask whether there is, overall, any evidence for a relative deficit in the location compared with the shape identity task for the PWS participants, and whether any differential deficits are associated with a particular form of PWS.

Method

Participants

Forty participants with PWS were recruited via the Prader-Willi Syndrome Association-UK; 28 (12 males; age: 6:10-18:7 years, mean: 13:5, SD: 3:3) showed a paternal deletion of chromosome 15, while 12 (4 males; age: 6:1-17:9 years, mean: 11:6, SD: 5:0) showed maternal uniparental disomy of chromosome 15. 28 boys with FraX with a full FMR1 mutation (9:2 –19 years; mean: 13:11, SD: 2:6) were recruited via the Fragile-X society and 28 typically developing (TD) children (11 males, age: 5:1-11:9 years, mean: 8:8, SD: 1:11) were recruited via primary schools. The FraX group was restricted to males due to the differences in both genotype and phenotype between males and females with the syndrome (Loesch, Huggins & Hagermann, 2004). Informed consent from parents and carers, and assent from children to participate was obtained. Most participants in all groups were of White Caucasian ethnic origin and of moderate to high socio-economic status. Individuals were

included only if they had a genetically confirmed classification of their diagnosis (PWS and FraX groups). From 30 appropriate individuals with deletion 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). Participants were tested in homes or schools or in Birmingham University. Ethical approval for the study was obtained from the University of Birmingham Ethical Review Committee.

Measures and procedure

The experimental tasks required participants to respond to either the location or the identity of a shape, presented via a lap top using E-prime® software (Psychology Software Tools Inc.,www.pstnet.com). Participants were positioned approximately 50cm away from the screen. Each trial consisted of a fixation cross for 1000ms, followed by the stimulus display which appeared until a response was made. There was then a blank interval of 500ms followed by the next trial. The stimulus display consisted of a single red square or blue circle (in a $5cm^2$ area), which was presented to one side of the participant's visual field (the centre of stimulus was 12cm away from fixation). Response options were provided on a standard keyboard (marked with stickers) and were a left side, red square key and a right side, blue circle key. The shape identity and location task types task types were administered in separate blocks (block order was counterbalanced across participants) of 32 trials each. Practise sessions were presented to ensure that the children understood what was required. Each task block included equal numbers of 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), and of each picture in each position. Asymmetry in task performance can

be demonstrated by absolute differences in reaction times (RTs) or error rates across the two tasks, but also by an interaction between task type and congruency, indicating that response interference (demonstrated when incongruent responses are slower than congruent responses: the congruency effect) is different between the two task types. Normally, response interference is greater when participants respond to the identity of a stimulus as opposed to its location (Simon, 1969).

In order to measure general cognitive functioning, we used a recognised short form of the *Wechsler Intelligence Scales for Children (WISC-III)* (Wechsler, Golombok & Rust, 1992) administering the similarities, vocabulary, block design and object assembly subscales according to the WISC manual (e.g., Mason, Humphreys & Kent, 2003).

Results

Part 1: Performance in the location and shape identity tasks in individuals with PWS deletion.

For this analysis, children with PWS deletion were compared to FraX and TD groups. 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. Across all WISC subtests typically developing children performed significantly better than PWS deletion individuals, who performed significantly better than individuals with FraX (see Appendix A). This reflects the previously reported levels of intellectual disability in the two syndromes (e.g. Whittington et al., 2004; Alanay et al., 2007). 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 ages of the two syndrome groups ($t(54)= 0.68$, $p= .50$).

Mean reaction times for correct response trials were analysed using mixed effects ANCOVAs with group (PWS deletion, FraX, TD) as the between subjects factor, and task type (identity, location) and congruency (congruent, non-congruent) as within subjects factors. Chronological age was treated as a covariate in this analysis in order to control for amount of life experience. In the ANCOVA comparing all three groups, there was a significant main effect of group ($F(2,80)=15.67$, $p< .001$) and a significant task * group interaction ($F(2,80)=4.98$, $p= .009$), but there was no significant interaction between task, congruency and group. The interaction between group and task type remained significant in all two group comparisons (PWS deletion vs. TD: $F(1,53)=11.12$, $p= .002$; FraX vs. TD: $F(1,53)=4.82$, $p= .033$; PWS deletion vs. FraX: $F(1,53)=4.14$, $p= .047$). These interactions (see Figure 1) resulted from a significant RT advantage for location trials over identity trials in the TD group ($t(27)=6.77$, $p< .001$), but the unusual pattern of RT advantages for identity trials over locations trials in both the PWS ($t(27)= -2.12$, $p= .043$) and FraX ($t(27)= -2.32$, $p= .028$) groups. This suggests that children with deletion PWS and boys with FraX showed a significantly greater deficit relative to typically developing children in the location task compared to the identity task. However, there was no significant group difference in the effect of executive control (congruency) between the two task types (i.e., no interactions with congruency).

Figure 1 about here

Considering the group differences in general intellectual functioning as measured with the WISC, we repeated the above analysis including WISC vocabulary score as a covariate. This allowed us to assess the relationship between general level of intellectual functioning and the reported increased deficit in location verses identity tasks in the syndrome groups relative to the TD group. The ANCOVA across all three groups showed no significant interaction between group and task ($F(2,79)=2.26$, $p= .11$), although there was a significant main effect of group ($F(2,79)=4.93$, $p= .01$). This suggests that the increased deficit relative to TD children in location processing verses identity processing in the children with PWS deletion and FraX shows an association with general intellectual ability.

The mean proportion of correct responses in location and identity shape tasks across PWS deletion, FraX and TD groups are shown in Figure 2. The proportions of correct responses were transformed using an arcsine transformation (inverse sine of the square root of the value), which can be applied to proportional data that shows a binomial distribution (as in correct/ incorrect accuracy data) in order to improve its normality (Chang, 2006). Mixed effects ANCOVAs with age and WISC vocabulary score as covariates were applied to the arcsine transformed accuracy data. Considering PWS deletion, FraX and TD groups, there was a significant main effect of group ($F(2,79)=11.17$, $p< .001$) and a significant interaction between group and task ($F(2,79)=10.14$, $p< .001$). There was also a significant task*congruency interaction ($F(1,79)=12.58$, $p= .001$), but no interactions involving congruency and group. The group*task interaction remained significant in all two group comparisons

(PWS deletion vs. TD: $F(1,52)=8.08$, $p= .006$; FraX vs. TD: $F(1,52)=13.84$, $p< .001$; PWS deletion vs. FraX: $F(1,52)=4.33$, $p= .042$). In support of the results from the analysis of RTs, these interactions (see Figure 2) resulted from significantly more accurate performance in the location task compared to the identity shape task in the TD group ($t(27)= -3.50$, $p= .002$), but significantly more accurate performance in the identity shape task compared to the location task in both PWS deletion ($t(27)=2.56$, $p= .016$) and FraX groups ($t(27)=6.67$, $p< .001$). Additionally, it is interesting to note that accuracy on the identity shape task was actually higher in the PWS deletion and FraX groups than in the TD group, an effect that approached significance in PWS deletion verses TD ($t(54)=1.86$, $p= .068$). For each of these separate analyses between groups there were also significant task*congruency interactions (PWS vs. TD: $F(2,79)=11.17$, $p< .001$; FraX vs. TD: $F(2,79)=11.17$, $p< .001$; PWS vs. FraX: $F(2,79)=11.17$, $p< .001$), but none of these were qualified by further interactions with group.

Figure 2 about here

Part 2: Comparison of the PWS UPD and PWS deletion genetic subtypes on identity shape and location tasks.

Performance on the WISC was used to individually pair participants with deletion PWS to each participant with UPD PWS based on separate matching of i) raw scores on the vocabulary subtest and ii) raw scores on the block design subtest. Of 24 pairs of participants, 20 were matched within 5 raw score points and the remainder within 13 raw score points. This resulted in three groups (UPD, deletion-verbal & deletion-nonverbal), which are described in Table 1. There were no significant differences in

age or WISC subtest scores between any of the groups, but trends were as expected, indicating that the deletion-verbal group showed higher non-verbal ability than the UPD group, but the deletion-nonverbal group showed lower verbal ability than the UPD group.

Table 1 about here

Mean RTs for correct trials (shown in Table 2) were analysed in two mixed effects ANOVAs with task and congruency as within subjects factors and group as the between subjects factor; comparing i) UPD and deletion-verbal groups and ii) UPD and deletion-nonverbal groups. There were no significant main effects of group or interactions between group, task type or congruency in either of the comparisons.

Table 2 about here

The proportions of correct responses were transformed using an arcsine transformation and analysed using ANOVAs. Considering the UPD and deletion-verbal groups, there was no significant main effect of group or interactions between group, task type or congruency. However, in the comparison of the UPD and deletion-nonverbal groups there was a significant interaction between group and task: $F(1,22)=5.25$, $p= .032$ (despite no significant main effect of group). This interaction (see Figure 3) resulted from more accurate performance in the location task compared to the identity shape task in the UPD group, but significantly more accurate performance in the identity shape task compared to the location task in the deletion nonverbal group ($t(11)=2.89$, $p= .015$). However, as shown in Figure 3, most of the group*task type interaction appears to occur on non-congruent trials, and indeed the

task*congruency*group interaction bordered on significance ($F(1, 22)=3.84$, $p= .063$). The tendency for the task effect to emerge most strongly on incongruent trials may be expected as it is on incongruent trials when the 'stronger' dimension (whether that be location or identity shape depending on the individual) may be signalling an inappropriate response.

Figure 3 about here

Discussion

In Part 1 of our analysis we assessed performance on tasks requiring judgements about the locations and identities of simple visual shapes in individuals with PWS. The task requiring selection of the locations of the stimuli should emphasise dorsal stream processing (Schumacher et al., 2006, 2007), while the shape identification task should emphasise more ventral visual processing (Wittforth et al., 2006). In agreement with previous findings indicating a specific deficit in dorsal stream processing in individuals with FraX (Kogan et al., 2004), we showed that a group of boys with FraX were more impaired relative to typically developing children in the location, compared to the shape identity task. This provides confirmatory evidence that the location task 'taps' dorsal stream processing. Children with the deletion subtype of PWS showed a similar pattern of performance, with there being a greater deficit in the location task relative to the shape identity task. Despite reported deficits in executive functioning in individuals with FraX and PWS (Stauder et al., 2005; Wilding, Cornish & Munir, 2001; Woodcock et al., sub a), we found no evidence that executive deficits had a differential effect on location and identity task performance in

these groups compared with the controls, as none of the interactions involving group as a factor were qualified by interactions with response congruency. For the RT measure, the contrast between the location and identity tasks in individuals with PWS deletion and FraX, relative to typically developing individuals, was eliminated when we statistically controlled for differences in a measure of verbal ability. However, the effects on errors remained, with PWS and FraX individuals making more errors on the location than the shape task and the opposite pattern occurring for TD individuals.

In Part 2 we conducted a more specific comparison between individuals with different forms of PWS. Children with UPD showed no significant differences in location or identity shape task performance when compared to children with a chromosome 15 q11-13 deletion who were matched on a measure of verbal ability. When compared to children with a deletion matched on a measure of non-verbal ability, children with UPD showed relatively better performance in the location task along with a deficit in the shape identity task. These differences tended to be most pronounced on incongruent trials (Figure 3), when the two dimensions offered conflicting information.

Location verses shape discrimination in PWS

Despite reported strengths in visual processing in individuals with deletion PWS (e.g. Dykens, 2002), our results suggest that these individuals showed a particular deficit in a location discrimination task which typically developing individuals find relatively easy. This suggests that, considered as a single factor, visual processing is *not* a strength in PWS deletion compared to typically developing children, though it remains possible that individuals with PWS deletion show a strength in visual

processing relative to other aspects of cognitive functioning. Our results do suggest however, that any relative strength would lie in visual processing mediated by the ventral stream (evidenced by the shape discrimination task) as opposed to the dorsal stream (evidenced by the location discrimination task). Indeed, it is interesting to note that the PWS deletion group tended to perform even more accurately than the TD children on the identity task, which would be consistent with the PWS deletion group having a specific strength in ventral stream processing.

In addition to assessing location and shape identification, the tasks we used placed differential demands on executive control when the irrelevant dimension was incongruent with the response to the stimulus defined along the relevant dimension. Interestingly, there was no significant difference between FraX, PWS and TD children in the way the executive control demands affected performance across the identity and location task types, as the effects of task did not interact with response congruency. This suggests that the particular deficit in the location task apparent in individuals with PWS and FraX was not a result of differential effects of executive dysfunction across the two types of task. Nevertheless, when we statistically controlled for general intellectual ability using a measure of verbal ability, the group differences between the location and the identity shape task on RTs were no longer significant. This suggests a relationship between specific deficits in dorsal stream functioning and general intellectual functioning. A similar finding was reported by Atkinson et al. (2003) who showed that after controlling for a measure of vocabulary, dorsal stream functioning did not appear to be more deviant than ventral stream functioning in children with Williams syndrome. The relationship is also supported by the present results showing increased location task deficits in the FraX group

compared to the PWS deletion group, when the FraX group were more intellectually disabled. These results can be accounted for if a deficit in dorsal processing can cause poor performance on tests of intellectual functioning. Note, though, that the differential errors on the location compared with the identity task in the PWS and FraX groups remained, even with effects of vocabulary accounted for, so the contrast between the tasks occurs over and above variations that relate to more general intellectual functioning.

It has been argued that dorsal stream functioning improves with increasing chronological age (Atkinson et al., 1997; Spencer et al., 2000) and that the specific deficit associated with various developmental disorders is generally evidenced by increased variability in functioning across individuals, with some individuals showing no notable deficit (e.g. Atkinson et al., 2003). It would therefore be interesting in future to investigate the degree with which the apparent variation in dorsal stream functioning found here may be associated with variation in general intellectual functioning in the PWS population.

A comparison of PWS sub-types

When matched to children with a chromosome 15 q11-13 deletion individuals on a measure of non-verbal ability (also close verbal ability), UPD individuals showed better performance on the location task, along with worse performance on the shape identification task. These effects were strongest on incongruent trials, when the location response required was contradicted by the response to the identity of the stimulus. It is possible that these group differences may have been linked to differential effects of executive control processes on the two different types of task,

and so emerged on incongruent trials. This would fit with the idea that UPD verses deletion group differences lie specifically in the differential effect of executive control processes on dorsal verses ventral stream visual processing, with UPD individuals having poor executive control over ventral stream (shape identification) tasks while deletion individuals show the opposite pattern (poor executive control over dorsal stream processing, in the location task). Perhaps, similar to the suggestion by Atkinson et al. (2003), this group difference may result from differences in specific frontal sub circuits involved in spatial and non-spatial behaviour, or in the connectivity between frontal and parietal/ temporal systems. Irrespective of how far executive control processes may have interacted with identity shape and location task performance across the two groups, the present findings suggest that even the relatively small genetic differences between UPD and deletion PWS may be associated with differential effects on aspects of dorsal and ventral stream processes.

When matched on a measure of verbal ability, the UPD children showed no significant differences compared to deletion children in performance on the identity shape or location tasks. It is interesting to note this deletion group showed better performance than the UPD group on a measure of non-verbal ability; an effect that was bordering on significance. This is what we would expect based on previous research (e.g. Roof et al., 2000), as UPD individuals generally show better verbal than non-verbal abilities, and deletion individuals generally show better non-verbal than verbal abilities. Therefore, it is possible that group differences in general non-verbal abilities may have masked group differences in performance across identity shape and location tasks. In fact, when comparing the individuals with UPD to those with a deletion matched for verbal ability, the same trends were evident as when comparing

UPD and deletion individuals matched for non-verbal ability: in non-congruent trials the UPD group showed better performance in the location task and the deletion individuals showed better performance in the identity shape task.

Limitations

It should be noted that the typically developing children were significantly younger than those with PWS deletion and FraX. This would be a potential limitation if we were aiming to report on the absolute size of a deficit in dorsal stream functioning in the PWS deletion and FraX groups. However, we have reported a relative deficit in dorsal stream functioning compared to ventral stream functioning in these groups, and considering that (as discussed above) dorsal stream functioning typically improves with age, the age difference between the groups provides additional support for there being a dorsal stream deficit following PWS deletion. It should also be noted that as our group of children with FraX was entirely male, we are unable to extend our results to females with FraX, and our results are unable to inform on the potential affect of gender per se on dorsal stream functioning. However, there are important genetic and phenotypic differences between males and females with FraX (e.g. Loesch et al., 2004) which led us to constrain our FraX sample to males. Future research investigating the potential differences between males and females with FraX in dorsal stream functioning would be interesting, particularly considering the known differences in genetic and neuroanatomical abnormalities (e.g. Eliez, Blasey, Freund, Hastie & Reiss, 2001). Finally, the present findings are restricted to children, and are therefore unable to inform on the developmental trajectory of visual functioning in PWS, or if the deficit in dorsal stream functioning in individuals with deletion PWS remains present in adults with the syndrome: it would be interesting to investigate this

trajectory, particularly in light of its potential relationship with general intellectual ability.

References

Alanay, Y., Unal, F., Turanli, G., Alikasifoglu, M. & Alehan, D. et al. (2007). A multidisciplinary approach to the management of individuals with fragile X syndrome. *Journal of Intellectual Disability Research, 51*, 151-161.

Atkinson, J., Braddick, O., Anker, S., Curran, W., Andrew, R., Wattam-Bell, J. et al. (2003). Neurobiological models of visuospatial cognition in children with Williams syndrome: Measures of dorsal-stream and frontal function. *Developmental Neuropsychology*, *23,* 139-172.

Atkinson, J., King, J., Braddick, O., Nokes, L. & Anker, S. et al. (1997). A specific deficit of dorsal stream function in Williams´ syndrome. *Cognitive Neuroscience and Neuropsychology,* 8, 1919-1922.

Bertella, L., Girelli, L., Grugni, G., Marchi, S. & Molinari, E. et al. (2005). Mathematical skills in Prader-Willi Syndrome. *Journal of Intellectual Disability Research, 49,* 159-169.

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.

Bruno, N., Bernardis, P., & Gentilucci, M. (2008). Visually guided pointing, the Muller-Lyer illusion, and the functional interpretation of the dorsal-ventral

split: Conclusions from 33 independent studies. *Neuroscience and Biobehavioral Reviews, 32,* 423-437.

Chang, S. W. (2006). Methods in scaling the basic competence test. *Educational and Psychological Measurement, 66,* 907-929.

Dykens, E. M. (2002). Are jigsaw puzzle skills "'spared" in persons with Prader-Willi syndrome? *Journal of Child Psychology and Psychiatry, 43,* 343-352.

Eliez, S., Blasey, C. M., Freund, L. S., Hastie, T., & Reiss, A. L. (2001). Brain anatomy, gender and IQ in children and adolescents with fragile X syndrome. *Brain, 124,* 1610-1618.

Fox, R., Yang, G. S., Feurer, I. D., Butler, M. G., & Thompson, T. (2001). Kinetic form discrimination in Prader-Willi syndrome. *Journal of Intellectual Disability Research, 45,* 317-325.

Fu, Y. H., Kuhl, D. P. A., Pizzuti, A., Pieretti, M. & Sutcliffe, J. S. et al. (1991). Variation of the CGG Repeat at the Fragile-X Site Results in Genetic Instability - Resolution of the Sherman Paradox. *Cell, 67,* 1047-1058.

Ganel, T. & Goodale, M. A. (2003). Visual control of action but not perception requires analytical processing of object shape. *Nature, 426,* 664-667.

Hansen, P. C., Stein, J. F., Orde, S. R., Winter, J. L., & Talcott, J. B. (2001). Are dyslexics' visual deficits limited to measures of dorsal stream function? *Neuroreport, 12,* 1527-1530.

Hoeft, F., Barnea-Goraly, N., Haas, B. W., Golarai, G., Ng, D., Mills, D. et al. (2007). More is not always better: Increased fractional Anisotropy of superior

longitudinal fasciculus associated with poor Visuospatial abilities in Williams syndrome. *Journal of Neuroscience, 27,* 11960-11965.

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.

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.

Melara, R. D., Wang, H., Vu, K. P., & Proctor, R. W. (2008). Attentional origins of the Simon effect: Behavioral and electrophysiological evidence. *Brain Res, 1215*.

Milner, A. D. & Goodale, M. A. (2008). Two visual systems re-viewed. *Neuropsychologia, 46,* 774-785.

Mishkin, M & Ungerleider, L. G. (1982). Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. *Behavioural Brain Research, 6,* 57-77.

O'Brien, J., Spencer, J., Atkinson, J., Braddick, O. & Wattam-Bell, J. (2002). Form and motion coherence processing in dyspraxia: evidence of a global spatial processing deficit. *Cognitive Neuroscience,* 13, 1399-1402.

Pisella, L., Binkofski, F., Lasek, K., Toni, I., & Rossetti, Y. (2006). No double-dissociation between optic ataxia and visual agnosia: Multiple sub-streams for multiple visuo-manual integrations. *Neuropsychologia, 44,* 2734-2748.

Psychology Software Tools Inc. (1996-2003). E-prime® (Version 1.1) [Computer software]. Pittsburgh, USA.

Roof, E., Stone, W., MacLean, W., Feurer, I. D., Thompson, T., & Butler, M. G. (2000). Intellectual characteristics of Prader-Willi syndrome: Comparison of genetic subtypes. *Journal of Intellectual Disability Research, 44,* 25-30.

Rossetti, Y., Pisella, L., & Vogels, A. (2003). Optic ataxia revisited: Visually guided action versus immediate visuomotor control. *Experimental Brain Research, 153,* 171-179.

Schumacher, E. H. E. (2003). Neural Evidence for Representation-Specific Response Selection. *Journal of Cognitive Neuroscience, 15,* 1111-1121.

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.

Spencer, J., O'Brien, J., Braddick, J., Atkinson, O., Wattam-Bell, J., & Riggs, K. (2000). Form and motion processing in autism. *Perception, 29,* 98-99.

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.

Sturmer, B., Siggelkow, S., Reinhard, D., & Leuthold, H. (2000). Response priming in the Simon paradigm: A transcranial magnetic stimulation study. *Experimental Brain Research, 135,* 353-359.

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, Golombok and Rust (1992). *Wechsler Intelligence Scales for Children-Third Edition UK.* Psychology Corporation, UK.

Whittington, J., Holland, A., Webb, T., Butler, J. & Clarke, D. et al. (2004). Cognitive abilities and genotype in a population-based sample of people with Prader-Willi syndrome. *Journal of Intellectual Disability Research, 48,* 172-187.

Wilding, J., Cornish, K., & Munir, F. (2002). Further delineation of the executive deficit in males with fragile-X syndrome. [References]. *Neuropsychologia, 40,* 1343-1349.

Woodcock, K. A., Oliver, C. & Humphreys, G. W. (in review, a). 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.

Woodcock, K. A., Oliver, C. & Humphreys, G. W. (in review, b). Differences in specific behaviours and cognitive characteristics between genetic subtypes of Prader-Willi syndrome.

Table 1. Shows the descriptive characteristics of the UPD PWS group and the two deletion PWS groups individually matched to the UPD participants for i) WISC vocabulary score (deletion-verbal) and ii) WISC block design score (deletion-nonverbal). *T*-statistics and *p*-values are shown for comparisons between the groups.

	UPD	Deletion-verbal	Deletion-nonverbal	Comparison		
				UPD, Deletion-verbal	UPD, Deletion-nonverbal	Deletion-verbal , Deletion-nonverbal
Age (years) Mean (SD)	11:6 (5:0)	13:11 (3:6)	13:9 (3:0)	*t*(19.7)= -1.35, *p*= .192	*t*(18.1)= -1.31, *p*= .206	*t*(22)= .13, *p*= .902
Gender (male: female)	4:8	7:5	5:7	-	-	-
WISC Vocabulary Mean (SD)	19.25 (12.17)	18.42 (8.55)	17.17 (6.44)	*t*(22)= .19, *p*= .848	*t*(22)= .52, *p*= .605	*t*(22)= .40, *p*= .690
WISC Block Design Mean (SD)	10.75 (11.50)	19.00 (13.69)	12.25 (9.84)	*t*(22)= -1.60, *p*= .124	*t*(22)= -.34, *p*= .735	*t*(22)= 1.39, *p*= .179

*Table 2***.** Shows the means and standard deviations of reaction times for correct trials and the mean proportion of correct responses in identity shape and location tasks. Performance is shown in congruent and non-congruent trials and compared between UPD PWS, deletion-verbal and deletion-nonverbal groups.

Task	**Congruency**	Mean reaction time (ms), (SD) of RTs, mean proportion of correct responses		
		PWS, UPD	PWS, Deletion-verbal	PWS, Deletion-nonverbal
Identity	Congruent	1450.75 (806.24) *0.98*	1023.74 (365.44) *0.96*	1206.74 (399.28) *0.98*
	Non-congruent	1844.53 (970.91) *0.85*	1193.95 (462.33) *0.91*	1257.20 (505.98) *0.96*
Location	Congruent	1603.49 (809.19) *0.96*	1104.34 (583.57) *0.98*	1248.96 (367.52) *0.94*
	Non-congruent	1864.70 (1028.63) *0.90*	1310.36 (743.16) *0.87*	1401.20 (473.13) *0.69*

Figure 1. Shows the mean reaction times for children in PWS deletion, FraX and TD groups comparing identity shape and location task types across congruent (C) and non-congruent (NC) trials.

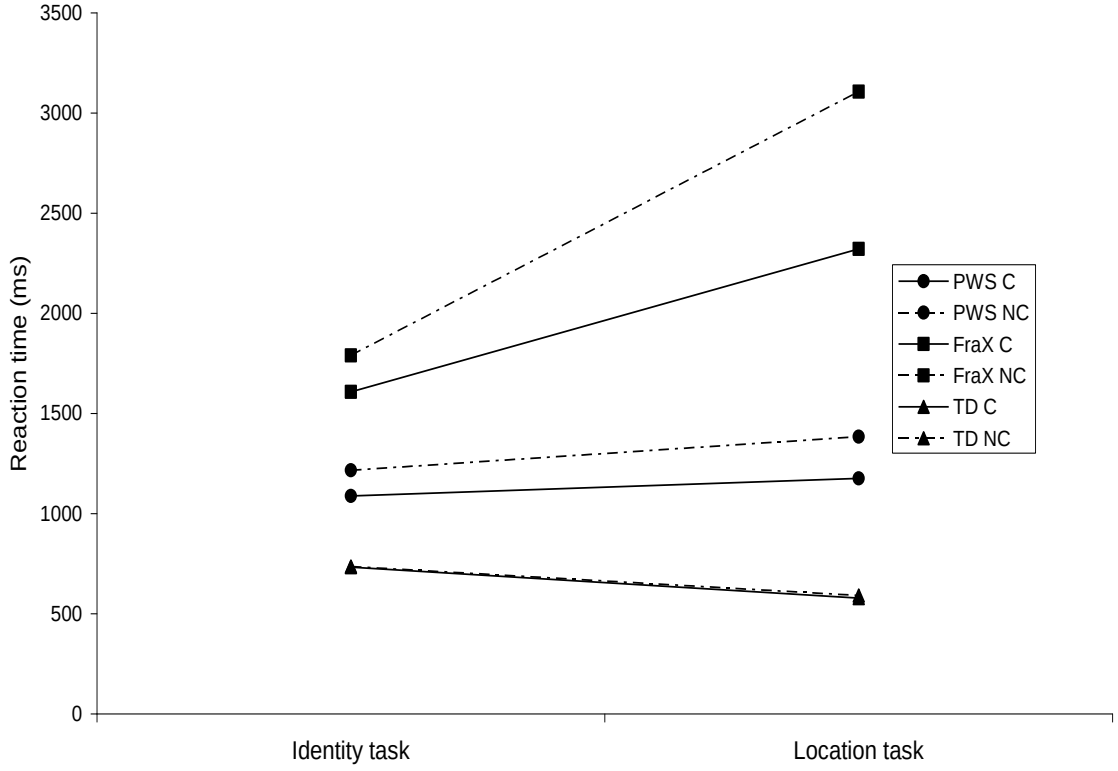

Figure 2. Shows the mean proportion of correct responses in the identity shape and location tasks across PWS deletion, FraX and TD groups.

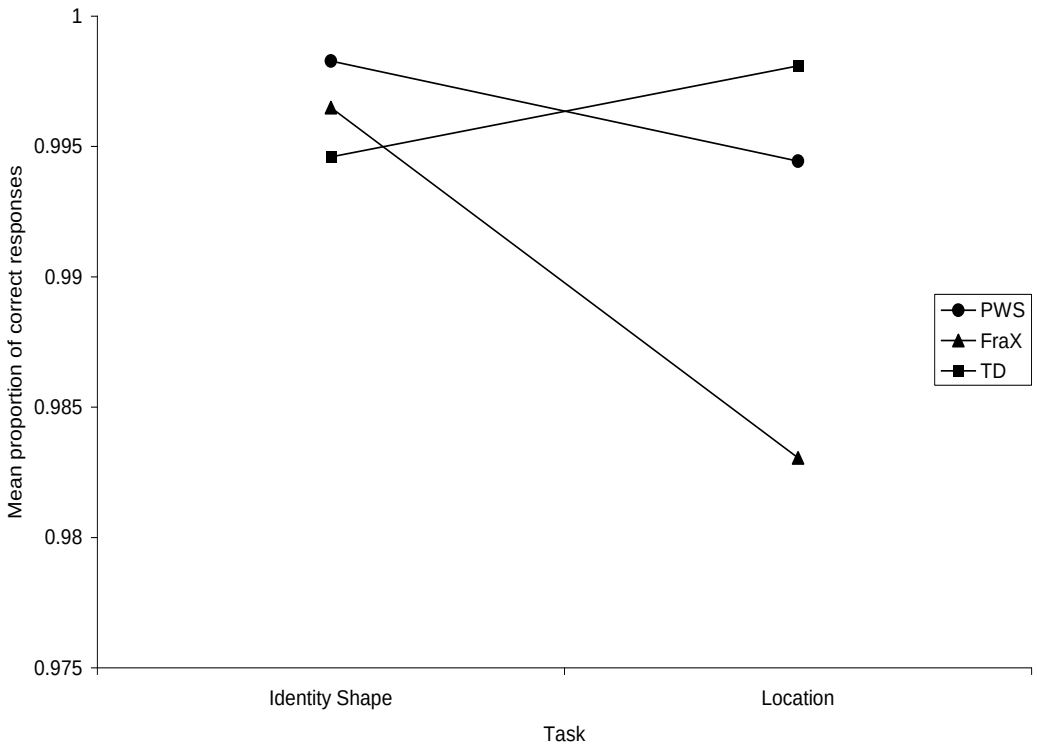

Figure 3. Shows the proportion of accurate responses in identity shape and location tasks across congruent and non-congruent trials, in PWS UPD and PWS deletion non-verbal groups.