NEURAL CORRELATES OF TASK SWITCHING IN PATERNAL 15Q11-Q13 DELETION PRADER-WILLI SYNDROME

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Task switching in PWS: neural correlates

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ABSTRACT

We report a first study of brain activity linked to task switching in individuals with Prader-Willi syndrome (PWS). PWS individuals show a specific cognitive deficit in task switching which may be associated with the display of temper outbursts and repetitive questioning. The performance of participants with PWS and typically developing controls was matched in a cued task switching procedure, and brain activity was contrasted on switching and non-switching blocks using fMRI. Individuals with PWS did not show the typical frontal-parietal pattern of neural activity associated with switching blocks, with significantly reduced activation in regions of the posterior parietal and ventromedial prefrontal cortices. We suggest that this is linked to a difficulty in PWS in setting appropriate attentional weights to enable task-set reconfiguration. In addition to this, PWS individuals did not show the typical pattern of deactivation, with significantly less deactivation in an anterior region of the ventromedial prefrontal cortex. One plausible explanation for this is that individuals with PWS show dysfunction within the default mode network, which has been linked to attentional control. The data point to functional changes in the neural circuitry supporting task switching in PWS even when behavioural performance is matched to controls and thus highlight neural mechanisms that may be involved in a specific pathway between genes, cognition and behaviour.

KEYWORDS

Prader-Willi syndrome, task switching, functional magnetic resonance imaging (fMRI), frontal-parietal neural activity, behaviour, default mode network

1 INTRODUCTION

Prader-Willi syndrome (PWS) is a genetic disorder associated with the absence of alleles of paternal origin within a critical region (q11-q13) on chromosome 15. The most common genetic mechanism for this abnormality is a paternal deletion within the critical region (60-70% of individuals), which can vary in size (Type 1 and Type 2 deletions). Maternal uniparental disomy of chromosome 15 is less common (approximately 25-30% of individuals), and chromosomal translocations and mutations of the imprinting centre can also cause PWS (Bittel et al., 2006). Estimates of the PWS population prevalence rate vary, but the lower bound is thought to be 1:52 000 (Whittington et al., 2001).

The cognitive profile of individuals with PWS is characterised by a downward shift in the distribution of IQ scores and mild to moderate intellectual disability (Whittington et al., 2004 a). However, the profile also comprises relative strengths and deficits in specific cognitive capacities: strengths in academic achievement and form-based visual processing (Dykens, 2002; Whittington et al, 2004 b), but deficits in action-based visual processing, auditory processing and mathematical skills (Bertella et al., 2005; Stauder et al., 2002; Woodcock & Humpreys et al., 2009). There is also some evidence for executive dysfunction, including deficient inhibition (Jauregi et al., 2007; Stauderet al., 2005; Walley & Donaldson, 2005), although the precise nature and specificity of these deficits has until recently, been relatively poorly described.

In a recent study, Woodcock & Oliver and Humphreys (2009 a) showed that individuals with a paternal deletion of chromosome 15 within the PWS critical region (deletion PWS) showed a deficit in task switching that appeared to be characterised by specific problems with task-set reconfiguration (one component of task switching) when compared to typically developing

individuals, even after controlling for the presence of an intellectual disability. Importantly, the deficit in task switching was associated with a clinically significant preference for routine and predictability, which was linked to a profile of challenging behaviours (temper outbursts and repetitive questions; Woodcock & Oliver et al., 2009 a, 2009 b, 2009 c). To date, the neural substrates of these changes in task switching have not been examined. In the present paper we report the first brain imaging study addressing this question.

Brain structure and function in PWS has rarely been examined. One study reported on five participants with slight ventriculomegaly, cortical atrophy and small brain stem (Hashimoto et al., 1998). Another reported ventriculomegaly in 20 individuals, and reduced parietal-occipital lobe volume, incomplete insula closure and sylvian fissure polymicrogyri each present in about half of the participants (Miller et al., 2007). Another study reported white matter lesions in six out of 17 participants, but the location of these was not consistent across participants (Miller et al., 2006). A Diffusion Tensor Imaging study pointed towards abnormalities in brain diffusivity in the frontal white matter and some subcortical structures such as the thalamus (Yamada et al., 2006). Therefore, while it appears that at least some individuals with PWS do show slight brain structural abnormalities there is no evidence to date to suggest consistent and systematic alterations in brain structure. Prior functional brain imaging has been limited to studies of the neural responses to hunger and satiety in PWS individuals (hyperphagia is characteristic of the syndrome, Hinton, Holland et al., 2006; Hinton et al., 2006; Holsen et al., 2006; Shapira et al., 2005). However, a few functional imaging studies have investigated neural correlates of specific executive deficits in other genetic neurodevelopmental disorders. Many genetic neurodevelopmental disorders (including the disorders assessed in these functional imaging studies and PWS) are associated with profiles of abnormal executive functioning and reductions in the level general cognitive functioning. Thus, this previous work provides a useful starting point for our investigation of PWS.

Previous functional imaging studies on executive functioning (including task switching, inhibition and updating paradigms) in genetic neurodevelopmental disorders known to be associated with executive deficits have included studies of people with Fragile X and Williams syndromes (Menon et al., 2000; Kwon et al., 2001; Tamm et al., 2002; Cornish et al., 2004; Hoeft et al., 2007; Mobbs et al., 2007). Although these studies report differences between task related neural activity in individuals with the syndromes and control participants, interpretation of the results is made difficult due to performance differences between the atypical and typical participants. When performance differences exist between groups it is difficult to judge if there is a qualitative deficit in a given brain area or if there is a general decrease in activity (not confined to the critical brain regions) which is observed in the critical regions due to their sensitivity to the task. In the present study we sought to overcome this potential problem by matching the behaviour of a group of individuals with PWS and a group of control participants under conditions of task switching.

Numerous functional imaging studies have examined task switching in typically developing participants. These have highlighted frontoparietal brain regions that are recruited when task switching takes place (Buchsbaum et al., 2005; Derrfuss et al., 2005; Wager et al., 2004). Different component processes involved in task switching have also been shown to activate different frontoparietal regions at different times during the task switch. Advance preparation for a switch following a cue is associated with lateral prefrontal activity, but, following the advance preparation period, switch related activity becomes focused within parietal regions (Brass et al., 2005; Kimberg et al., 2000; Luks et al., 2002; Ruge et al., 2005). This is consistent with the posterior parietal cortex being involved in implementing the task switch. The sustained control required while having to switch between tasks (the overall mixing cost), on the other hand, is associated with activity in the anterior cingulate, and medial and lateral anterior prefrontal cortices, which contrasts the activity in dorsal and ventrolateral prefrontal, and superior parietal regions that is linked to switching trials (switch costs; Braver et al., 2003).

There are also differences between the brain areas involved in contrasting switch tasks. Regions involved in switching visual attention between two features of stimuli (perceptual switching) have been dissociated from those involved in response switching, with perceptual switching associated with superior parietal regions (Ravizza & Carter, 2008), while the presupplementary motor area may play a critical role in response switching (Rushworth et al., 2002), and dorsolateral prefrontal areas are associated with switches of task rules (Ravizza & Carter, 2008). In contrast, activity in the orbitofrontal cortex may play a specific role in task switching based on feedback on previous responses (Hampshire & Owen, 2006) or in switching selection 'weights' to perceptual signals (Pollmann et al., 2007).

Switching between different types of stimuli and responses has also been associated with different patterns of frontoparietal activity. Extradimensional switching has been associated with activity in the ventrolateral prefrontal cortex (Hampshire & Owen, 2006). Switching between tasks involving bivalent stimuli (that afford both tasks) is associated with increased prefrontal activity relative to task switching involving univalent stimuli (Brass et al., 2003), and the presupplementary motor area may play a specific role in switching to a new bivalent rule (Crone et al., 2006). The location of activity within the anterior cingulate cortex has been shown to vary depending on whether switching to withholding a response (anterior) or switching to immediate responding (posterior: Swainson et al., 2003).

The previous behavioural studies on people with PWS have demonstrated that individuals with the syndrome show specific deficits in task switching that may be characterised by a particular problem in task-set reconfiguration. Difficulties in task switching have been linked to clinically significant behavioural problems (although within this cognition-behaviour association cognition has only been described at the level of the overall deficit in task switching, not at the level of any component

process that may be driving the switching problem). Due to the scarcity of previous studies on executive functioning in PWS and the complete absence of functional imaging investigations of executive functioning in individuals with the syndrome, here we employed a block design fMRI method to investigate whether individuals with PWS show differences in the pattern of neural activity associated with any aspect of performance on a visually cued task switching paradigm relative to typically developing control participants. Behavioural performance and brain activity was measured in switching blocks where there was switching between two tasks and non-switching blocks where only one task was performed within a block. Importantly we altered the tasks performed by the PWS and control participants (in accordance with our previous research and pilot experiments) in order to match the two groups of participants for performance. Any changes in brain activity in the PWS individuals relative to the controls would then suggest qualitative changes in neural activity and would not reflect differences in task difficulty.

Based on the previous literature reviewed above, we hypothesise that individuals with PWS will not show the typical pattern of activity in frontoparietal brain regions that is associated with switching blocks in typically developing individuals. In particular, we predict that individuals with PWS will show decreased activation associated with switching in these frontoparietal regions relative to typically developing controls. Given the suggestion of a specific deficit in task-set reconfiguration in individuals with PWS and the role of posterior parietal brain regions in task-set reconfiguration, we specifically expect that the PWS group will show decreased activation relative to typically developing controls in the posterior parietal lobes.

2 RESULTS

Behavioural Results

Behavioural data were collected during scanning sessions. The mean RTs and accuracy data (shown in Table 1) were analysed separately and an arcsine transformation was applied to the accuracy data to improve its normality (Chang, 2006). Group was treated as a within subjects factor, comparing pairs of participants matched for chronological age and gender. The effect of task mixing was assessed in four-way repeated ANOVAs with the factors block (switching, non-switching), task (location, identity), congruency (congruent, non-congruent) and group (typically developing; TD, PWS). For the RT data there were significant main effects of block ($F(1,6)=11.38$, $p= .015$) and congruency ($F(1,6)=56.92$, $p< .001$), with a significant congruency*group interaction ($F(1,6)=12.91$, $p= .011$). While the TD group showed a significant overall effect of congruency ($t(7)= 6.95$, $p< .001$), this effect was not significant in the PWS group ($t(7)= .436$, $p= .676$). However, there were no significant group differences in the effect of task mixing. The accuracy data also showed significant main effects of block ($F(1,7)=201.47$, $p< .001$) and congruency ($F(1,7)=7.95$, $p= .026$) but no other significant main effects or interactions.

[Table 1]

The effect of task switching (within switching blocks) was assessed in four-way repeated ANOVAs with the factors task, congruency, switch (switch, repeat trials) and group. For the RT data there were significant main effects of congruency ($F(1,6)=46.16$, $p< .001$) and switch ($F(1,6)=10.23$, $p= .019$) but no other significant main effects or interactions. The accuracy data also showed significant main effects of congruency ($F(1,7)=9.08$, $p< .020$) and switch ($F(1,7)=164.89$, $p< .001$),

but no other significant main effects or interactions. In summary, the task adaptations were successful in ensuring that there were no significant differences between individually matched pairs of TD and PWS participants on mixing or switching performance in the task-switching paradigm.

Imaging Results

To isolate brain activity associated with task switching and/or task mixing (this will be referred to as switch-related activation from here on in) we subtracted activity during non-switching blocks from activity during switching blocks. To isolate brain deactivation associated with task switching and/or task mixing (switch-related deactivation) we subtracted activity during switching blocks from activity during non-switching blocks (see Methods section). Figure 1 illustrates the switch-related activation and deactivation shown by the TD group and Figure 2 illustrates the switch-related activation and deactivation shown by the PWS group.

[Figure 1]

[Figure 2]

In order to describe the pattern of switch related activation and deactivation in terms of regions of activity that were, as far as possible, small enough not to span across known functionally dissociable areas, the thresholded activation and deactivation maps (thresholded to a corrected cluster significance of $p < .05$; see *Methods*) were divided into clusters of activity that were associated with a switch-related contrast Z-score greater than 3.0 and comprised more than 100 voxels. In this way Tables 2a and 2b show the significant switch-related activation and deactivation respectively demonstrated by the TD group. Table 3 shows the significant switch-related activation

demonstrated by the PWS group. The PWS group demonstrated no significant switch-related deactivation.

[Table 2a]

[Table 2b]

[Table 3]

As can be seen in Figure 1 and Tables 2a and 2b, the significant switch-related activation shown by the TD group includes pre-frontal, anterior cingulate and parietal regions, which is in agreement with previous functional imaging studies of task switching paradigms in the general population (Buchsbaum et al., 2005; Derrfuss et al., 2005; Wager et al., 2004). The TD group also demonstrated significant switch-related deactivation in regions of the medial pre-frontal cortex, superior frontal gyrus, paracingulate cortex and frontal poles. As shown in Figure 2 and Table 3, the significant switch related activation demonstrated by the PWS group is restricted to areas of the occipital lobes and precuneus.

Changes in brain activity between switching and non-switching blocks were compared across TD and PWS groups in a fMRIB Local Analysis of Mixed Effects model using paired t-tests that contrasted matched pairs of participants (thresholded to a corrected cluster significance of $p < .05$; see *Methods* section). Figure 3 illustrates the brain regions in which the switching block – non-switching block activity was significantly greater in the TD group relative to the PWS group (shown in violet) and those in which the switching block – non-switching block activity was significantly greater in the PWS group relative to the TD group (shown in green). In order to delineate these effects, the group difference maps were divided into clusters of activity that were associated with a group contrast Z-score greater than 3.0 and comprised more than 50 voxels. Mean percentage signal change values within each cluster associated with switching block and non-

switching block wave forms were extracted from the mean activity across the four scans for each participant using FEATquery and paired t-tests were conducted between the mean percentage signal change values for switching blocks and non-switching blocks within TD and PWS participants respectively (see Table 4 for TD>PWS contrast; see Table 5 for PWS>TD contrast).

[Table 4]

[Table 5]

Given the complexity of the group comparison, it is important to view these results alongside the maps of significant switch-related activation and deactivation in the TD and PWS groups discussed above. Looking at Figure 3 and Table 4 in combination with Figures 1 and 2 and Tables 2a and 3 (above), it can be seen that certain prefrontal and parietal cortical regions associated with significant switch-related activation in TD participants were also significantly more activated during switching in the TD group relative to PWS. These regions included areas of the left and right middle frontal and right inferior frontal gyri, and in line with our hypotheses, regions in the posterior parietal lobes (left posterior supramarginal gyri). It is notable that the PWS participants tended to show switch-related *de*activation of these regions.

There were also a number of subcortical brain areas including regions of the hippocampus, amygdala, putamen and thalamus, and a region in the temporal lobes that were associated with significantly greater switch-related activation in the TD group relative to the PWS group, which were not significantly activated during switching in the TD group (see Table 2a). This group difference therefore, is driven by the interaction between switch-related activation of these regions in the TD group and switch-related *de*activation in the PWS group.

From Figures 3 and Table 5 it can be seen that an anterior region in the left and right frontal poles showed significantly greater switch-related activation in the PWS group relative to the TD group. However, in light of the results shown in Figures 1 and 2 and Tables 2-3, it becomes apparent that this group difference was driven by the absence of significant switch-related *de*activation in the PWS group, which was demonstrated in the TD group. In fact, PWS participants tended to show switch-related activation of this region.

In summary TD individuals showed significant switch-related activation of prefrontal, anterior cingulate and parietal regions in line with previous literature, while individuals with PWS showed significant switch-related activation restricted to areas of the occipital lobe and precuneus. TD individuals also showed significant switch-related deactivation of regions of the medial prefrontal cortex, superior frontal gyrus, paracingulate cortex and frontal poles. A number of prefrontal and parietal regions were significantly more activated by switching in the TD group relative to the PWS group, including regions of the posterior parietal lobes. There was a significant group interaction in subcortical areas including regions of the hippocampus, amygdala, putamen and thalamus, and in a region in the temporal lobes, which was driven by switch-related activation in the TD group but deactivation in the PWS group. There was also a significant group interaction in a bilateral region in the anterior frontal poles. TD individuals showed significant switch-related deactivation of this region, which was not demonstrated by individuals with PWS who tended to show switch-related activation.

3 DISCUSSION

The present results provide the first demonstration that task switching is associated with different patterns of neural activity in individuals with PWS compared to typically developing individuals. We varied the characteristics of the stimuli presented in a task switching paradigm so that task mixing and switching performance did not differ significantly between the two groups. Under these conditions, changes in neural activity do not reflect task difficulty but rather the differential involvement of contrasting brain regions.

It was demonstrated that typically developing individuals showed a pattern of significant prefrontal, anterior cingulate and parietal activation coupled with deactivation in the medial prefrontal cortex, superior frontal gyrus, paracingulate cortex and frontal poles associated with task mixing/switching. This pattern of activation is strongly supported by previous functional imaging studies of task switching (Buchsbaum et al., 2005; Derrfuss et al., 2005; Wager et al., 2004). The switch-related deactivation of prefrontal and cingulate regions was less expected given that most previous studies of task switching focus on activation associated with switching and/or mixing. However, these results are in line with descriptions of the 'default mode network' which includes regions (prefrontal, cingulate, precuneus, parietal, temporal and subcortical) that are deactivated during cognitively demanding tasks and show high activity and functional connectivity during resting state (Broyd et al., 2009; Greicius et al., 2003; Mazoyer et al., 2001; Northoff et al., 2010; Sridharan et al., 2008).

The individuals with PWS showed a different pattern of significant changes in neural activity associated with switching/mixing, that was restricted to activation in regions of the occipital cortex and precuneus and no regions of deactivation. In line with our hypotheses, when the two groups of matched pairs of participants were compared directly, the typically developing participants showed significantly greater switch-related activation in frontal parietal regions, including the ventromedial prefrontal cortex (right and left middle frontal gyrus, the right inferior frontal gyrus) and the

posterior parietal cortex (left posterior supramarginal gyrus), relative to the participants with PWS. Parietal brain regions have been associated with late stage task switching processes following advance preparation (Brass et al., 2005; Kimberg et al., 2000), with a specific role of the posterior parietal cortex suggested in task-set reconfiguration (Crone et al., 2006). This fits with the idea that posterior parietal cortex may be critical in setting the appropriate 'weights' between stimuli and responses to enable the task-relevant properties of stimuli to be selected (Bundesen et al., 2005). It follows that PWS individuals have difficulty in setting appropriate weights to the task-relevant and irrelevant aspects of stimuli (linked to dysfunction within the parietal cortex), which fits in with our previous behavioural findings demonstrating a specific PWS deficit in task-set reconfiguration (Woodcock, Oliver et al. 2009 a).

In the ventromedial prefrontal regions the typically developing individuals showed significant switching/mixing related activation, but the PWS group tended to show deactivation. Activity in the ventromedial prefrontal cortex has been linked with the motivational (reward) aspects of behavioural control (e.g. Breiter et al., 2001). A recent study investigated the neural correlates of task switching in individuals with obsessive compulsive disorder showed that individuals with the disorder showed switching related deactivation in the ventromedial prefrontal cortex, which was not apparent in control participants (Gu et al., 2008). The authors argue that the increased activation of the ventromedial prefrontal cortex during repeat relative to switching conditions in OCD participants was indicative of a tendency to maintain the previous task set and occurred due to altered subjective reward contingencies of maintaining the previous task set or switching. Thus in addition to a specific difficulty in setting appropriate weights to task relevant and task irrelevant aspects of the stimuli during switching, individuals with PWS may show abnormalities in the reward circuitry associated with switching.

In addition to the group differences described above, there was a significant group interaction in regions of the hippocampus, amygdala, putamen, thalamus and temporal lobes (areas not highlighted in the map of significant switching/mixing related activation in the typically developing group). This interaction was driven by a difference in the direction of the activity changes between the typically developing group (activation) and the PWS group (deactivation). In this context it is useful to expand on our discussion of the default mode network. In addition to task-negative regions, this network has been shown to comprise task-positive regions (including prefrontal, parietal and supplementary motor areas) that show increased activity during cognitive tasks in a manner that is negatively associated with the attenuations in activity in the task negative regions[1] (Broyd et al., 2009; Damoiseaux et al., 2006; Northoff et al., 2010).

Although relatively little is known about the function of the default mode network, it is thought that both the connectivity within the network and how activity here interacts with stimulus/task induced activity are important in maintaining attentional control (e.g. Broyd et al., 2009). Dysfunction within this network has been demonstrated in numerous disorders including autism (Assaf et al., 2010), Fragile X syndrome (Menon et al., 2004) and Down syndrome (Reynolds et al., 2009) and this is also associated with cognitive capacities known to be impaired in individuals with the disorder (e.g. during a go-nogo task in individuals with Fragile X syndrome, known to be associated with inhibitory deficits). One plausible explanation for the present results is therefore that individuals with PWS show dysfunction within the default mode network leading to an unusual pattern of changes in resting state activity and synchrony between task-negative and task-positive regions in the network during switching/mixing.

[1] Although here we refer to task negative and task positive regions within the same "default mode" network the first descriptions of this network included only task negative regions and researchers frequently distinguish between task-negative and task-positive regions as comprising different networks. Recent evidence however, points towards task-negative and task-positive regions comprising a single network (Northoff et al., 2010).

In addition to the increases in switching/mixing related activity in the typically developing group compared to the PWS group, the PWS group showed significantly increased activation of an anterior region of the ventromedial prefrontal cortex (inferior, anterior frontal poles) relative to the typically developing group. This group interaction was driven by a significant switching/mixing related deactivation in the typically developing group that was not demonstrated by the PWS group. This provides support for the suggestion of dysfunction in the default mode network in individuals with PWS. In particular, in PWS individuals there was no attenuation of activity in a region in the default mode network that is usually significantly attenuated to allow switching/mixing to occur. It must be highlighted however, that as the present study did not include any analysis of resting state neural activity, the suggestion of dysfunction within the default mode network in individuals with PWS must be considered preliminary. Nevertheless, given the evidence of dysfunction within this network in multiple disorders and in the context of specific cognitive difficulties (e.g. Broyd et al., 2009) possible dysfunction here is an important avenue for future research.

The present study suggests that the specific cognitive deficit in task-set reconfiguration in individuals with PWS may be underpinned by neuronal dysfunction. We propose that the genetic characteristics of (paternal deletion) PWS have a downstream effect on neurodevelopment, such that neural networks of cognitive control and flexibility develop abnormally. Abnormal functioning of these neural networks is associated with the specific cognitive deficit in PWS. Previous research has reported an association between specific cognitive deficits in task switching and the display of PWS phenotypic behaviours including temper outbursts and repetitive questions, via environmental mechanisms (Woodcock et al. 2009 a, 2009 b, 2009 c). We suggest that the phenotypic behaviours may be linked to the underlying pathology in the functioning of specific aspects of the frontal parietal neural circuitry supporting task switching and its interaction with the functioning of other neural networks linked to cognitive control. These results have important implications for potential intervention strategies for challenging behaviour in PWS. Cognitive training programmes

administered to typically developing young children have increased the speed of development of aspects of executive attention and underlying neural mechanisms (Rueda et al., 2005). It is possible that cognitive training focussed on attention switching in individuals with PWS may influence neuronal function and have a beneficial affect on cognitive ability and behaviour.

Limiting aspects of the work

Due to the lack of previous studies investigating neuronal function associated with cognitive performance in PWS the present design investigated neural activity at the level of switching or non-switching blocks. As a result, the neural activity that we have labelled as 'switch-related' actually refers to activity associated with task switching and task mixing. However, this is the first study investigating cognitive function using fMRI in individuals with PWS and we believe that the potential benefits from employing an event-related design were outweighed by the need for highly detailed hypotheses that could have only been based on little relevant research within the syndrome.

In order to control for the presence of intellectual disability and overall performance differences between typically developing individuals and individuals with PWS, the switching tasks were adapted to match overall behavioural performance between the two groups. This approach allowed us to avoid problems that would be associated with attempting to match the PWS group to a (younger) typically developing group for intellectual ability (including confounds of comparing brains of different ages and logistical difficulties with scanning very young children). Our approach also overcomes problems in interpreting differences in brain activity when performance also differs. However, the approach does not allow us to argue for there being specific neuronal dysfunction only in individuals with PWS, since individuals with intellectual disability due to other causal factors were not tested. Deficits in switching have also been reported in individuals with FraX (Wilding et al., 2002; Woodcock et al., 2009 a) and there has been some indication of neuronal

dysfunction associated with these deficits (Cornish et al., 2004). Future research involving detailed comparisons of the neural correlates of task switching in different groups of individuals is needed in order to evaluate whether all disorders reflect a common underlying neural pattern.

The design of the present study did not allow any developmental phenomena to be examined in detail (for example by employing a large number of participants from a number of different ages along the developmental spectrum). Thus, it remains unclear whether the abnormalities in task switching performance and associated neural dysfunction shown in individuals with PWS represent deviant (atypically developing) or developmentally delayed processes. In addition to this, due to the characteristics associated with PWS including scoliosis that often requires treatment with metal pins in the spine, the sample size employed in the present study was fairly small. Future collaborative research should look to extend the present investigation into larger samples including in such a way that would allow the consideration of developmental trajectories.

4 EXPERIMENTAL PROCEDURE

Participants

The participants were eight right handed individuals (five males) with a chromosome 15 q11-q13 deletion causing PWS with a mean age of 20:7 years (SD: 9:2 years). Eight TD control participants were individually matched to the PWS participants for age and gender (TD mean age: 21:0 years; SD: 8:11 years; $t(14)= .108$, $p= .916$). Table 6 shows the matched pairs of PWS and TD participants. The participants were recruited via a researcher held database, via the Prader-Willi Syndrome Association UK (PWS participants only) and via advertisements in the University of Birmingham (control participants only). Following initial screening, only those participants who met the necessary MRI safety criteria, who could easily read the words ‘what’ and ‘where’, and

who expected that they would be able to remain still for the period of an hour were invited to participate. Ethical approval for the study was obtained from the University of Birmingham Ethical Review Board.

[Table 6]

Stimuli, tasks and procedure

Two tasks were presented in switching blocks (both types of task) and non-switching blocks (one type of task per block). In the identity task participants made a response based on the shape and/or colour of the target, while in the location task participants made a response based on the position of the target relative to the centre of the display. All stimuli were presented on a white background. Each trial began with a central fixation cross, followed by a cue, and followed by a target with the cue remaining visible.

Each task was indicated by one of two possible cues (each cue included a written word and a symbol to assist understanding). This was necessary to allow us to control for the changing visual properties of the cue that necessarily occurred within switching blocks (because of the changes in task). Thus, within each switching block (see Figure 4) only one style of cue to each of the tasks was presented (the style of cue was counterbalanced across different switching blocks). In this way the visual properties of the cue changed (to a cue a different task) when the task changed but did not change for any other reason. In order to ensure that the visual properties of the cue changed equally within switching and non-switching blocks, within each non-switching block (see Figure 5) both styles of cues to the relevant (single) task were presented. The cue style changed (the visual properties of the cue) at the same frequency as that with which the visual properties of the cue changed (task switches) within switching blocks.

[Figure 4]

[Figure 5]

Importantly, to match PWS and TD groups on overall task performance, the shape/colour and relative position of the target stimuli presented to the two groups was adapted in order to decrease overall task performance by the TD group relative to if they had been presented with the same target stimuli as the PWS group[2]. Thus, one set of stimuli was presented to PWS participants (Figures 4 & 5) and a *different* set of stimuli (differing only in the shape/colour and relative positioning of the targets and the shape/colour of the corresponding response options) was presented to TD participants (see Figure 6). The overall effect of this manipulation was that TD participants were presented with location and identity tasks that were more difficult than those presented to PWS participants (the two locations were closer together and the two targets were less distinct from each other in shape/colour) but importantly, the relationship between the two tasks was exactly the same for both sets of stimuli.

[Figure 6]

Therefore, for PWS participants, targets consisted of a red circle or a blue square that could each be presented to the left or to the right of midline. For TD participants, targets consisted of a light blue circle or a dark blue circle that could each be presented slightly to the left or slightly to the right of midline. Response options for each group of participants were always the same (PWS: left red circle, right blue square; TD: left light blue circle, right blue circle). A schematic representation of

[2] The adaptations of the target stimuli for TD participants were developed with reference to the mean differences in RTs between PWS and TD participants on a similar task used in our previous research (Woodcock et al., 2009 a). Pilot experiments presented the fMRI task procedure on a standard computer to TD individuals. Each pilot participant completed the procedure with the PWS target stimuli and with a series of adapted target stimuli (different colours, positions, shapes). The final TD task stimuli were those that were associated with the necessary increase in mean RTs relative to RTs for the PWS target stimuli.

the response options was displayed throughout fMRI acquisition in order to reduce the demand on working memory.

Participants responded with the index and middle fingers of their right hand using two buttons on a button box resting in a comfortable position on their mid torso. Instructions were given to participants in a practise session prior to the imaging being carried out. Participants were told that the rectangle at the bottom of the screen represented the buttons that they could press and that they must read the word at the top of the screen to tell them what to do. When the word 'where' appeared participants must press the button on the same side as where the picture appeared (location task), but when the word 'what' appeared they must press the button that showed the same picture as the picture that appeared (identity task). Participants were told that the same instructions applied throughout and so were not informed which blocks would involve task switches.

Each block contained sixteen trials, in switching blocks six of these were switch trials. Within switching blocks, trials were presented in a pseudorandom sequence which comprised a combination of single repeat trials (x3; e.g. identity trial [I], location trial [L]), two repeat trials (x2; e.g. I, I, L), or three repeat trials (x1; e.g. I, I, I, L) before the switches (six switches in each block), making switches unpredictable. The type of task to be presented first within each switching block was counterbalanced across blocks. Congruent (PWS: red circle on the left, blue square on the right; TD: light-blue circle on left, blue circle on right) and non-congruent trials were evenly divided within blocks and within switch and repeat trials in switching blocks. Non-congruent trials were presented in addition to congruent trials to ensure that participants were necessarily required to switch between the two tasks and could not rely on a strategy that involved no switching to ensure correct performance (e.g. 'respond with a right side button if the stimulus is on the right or is a blue square/circle'). Each target was presented four times in each position within each block. Stimuli were presented using E-prime® software (Psychology Software Tools Inc.,www.pstnet.com).

Each participant took part in four fMRI sessions. During each session, four blocks were presented with 20s of fixation between each block and at the beginning and end of the session. Two switching and two non-switching blocks (one location and one identity task) were presented alternately. The type of cue (1 or 2) presented in each switching block and the type of cue presented first in each non-switching block was counterbalanced across blocks within each session. The order of blocks (switching/ non-switching (identity/ location)) was counterbalanced across sessions and each participant was randomly allocated to one of the 24 possible session orders. Practise sessions followed the same procedure as fMRI sessions but took place in a quiet room using a laptop for task presentation. Verbal feedback was given to assist with learning of the tasks. Participants completed between three and five practise sessions until they felt comfortable with the tasks, followed by another session in a mock scanning environment.

fMRI data acquisition

Images were obtained on a Philips 3T Achieva system using a SENSE head coil. Functional images were acquired using an Echo Planar pulse sequence (65º flip angle; 34ms echo time; 2000ms repetition time) with thirty four transverse 3mm slices, a 64x64 matrix and a 192x192x102 Field of View (voxel size: 3x3x3mm). Each fMRI session (scan) thus comprised 130 volumes. A high resolution (1x1x1mm) T1 weighted anatomical image was acquired within the same scanning session as the fMRI data comprising 160 sagital slices (flip angle: 8º; TE: 3.4ms; TR: 8.4ms).

fMRI preprocessing and analysis

fMRI Expert Analysis Tool (FEAT) version 5.92 from the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl) was used for fMRI preprocessing and analysis. The same series of preprocessing steps was applied to each scan before further analysis. The first ten volumes (20s) were deleted from the scan to ensure that steady state imaging had been reached before any of the data that would be analysed had been acquired. Motion correction using FMRIB's Linear Image Registration Tool (MCFLIRT; Jenkinson et al., 2002) was used to correct for participants' head movements. Average head movement was small during all scans; the mean displacement was .21mm (range: .09 - .55) for TD participants and .30mm (range: .06 - .87) for PWS participants. Slice timing correction was then applied that employed Fourier-space time-series phase-shifting and non-brain tissues were removed using the Brain Extraction Tool (BET; Smith, 2002). The images were spatially smoothed using a Gaussian smoothing kernel of FWHM: 5mm and all volumes were intensity normalised using a single scaling factor. Finally, high pass temporal filtering (Gaussian-weighted least-squares straight line fitting) with sigma of 60s was applied. Following this, participants' functional images were registered to their own high resolution T1 weighted anatomical image (from which non-brain structures had been removed using BET) and then to a standard MNI-space image using FLIRT (Jenkinson & Smith, 2001; Jenkinson et al., 2002).

First level analysis was carried out on the time series data from each scan using FMRIB's Improved Linear Modelling (FILM: Woolrich et al., 2001). FILM prewhitening ensured that statistics were valid and maximally efficient. The model included two square wave forms that matched the on-off stimulation pattern for 1) switch and 2) non-switch blocks, convolved with the FSL default FLOBS (FMRIB's Linear Optimal Basis Set: Woolrich et al., 2004; a set of basic functions that have optimal efficiency for covering the range of hemodynamic response function shapes that is likely to be shown in the data). Motion parameters estimated from MCFLIRT motion correction were added to remove any residual effects of head motion and the temporal filtering applied to the scans during preprocessing was also applied to the model. Z statistic images were produced for the switch –

non-switch and non-switch – switch contrasts of interest (thresholded using clusters determined by Z > 2.3, which is equivalent to a corrected cluster significance threshold of $p < .05$: Worsley, 2001).

The mean activation for each participant (across the four scans) was calculated in a second level analysis using a fixed effects model in FLAME (FMRIB's Local Analysis of Mixed Effects: Beckmann et al., 2003; Woolrich et al., 2004), which forced random effects variance to zero. All participants from one group were entered into one of two second level analyses to make the estimation of cross-session variance more robust by assuming that it was the same for all participants in the same group. These higher-level analyses were carried out using mixed effects models in FLAME and resulted in four contrasts of interest, the mean switch – non-switch and the mean non-switch – switch contrasts for the TD group and for the PWS group. Higher-level analysis was carried out using mixed effects models in FLAME and paired t-tests (matched pairs of participants) to compare across groups.

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TABLES

Table 1 shows the means and standard deviations of RTs and the proportion of accurate responses for non-switching and switching blocks across location and identity tasks. Performance is compared between PWS and TD control groups across congruent and non-congruent, switch and non-switch trial types.

Block	**Task**	**Congruency**	**Switching**	**TD**	**PWS**
				Mean RT(ms) **(SD)** ***Proportion of accurate responses***	
Non-switching blocks	Identity	Congruent		684.39 (90.13) *.95*	699.71 (169.71) *.80*
		Non-congruent		779.55 (116.87) *.93*	927.18 (247.71) *.72*
	Location	Congruent		637.78 (114.21) *.96*	682.60 (183.67) *.81*
		Non-congruent		754.37 (249.33) *.83*	721.58 (143.81) *.79*
Switching blocks	Identity	Congruent	Switch	803.90 (168.91) *.58*	776.16 (266.41) *.46*
			No-switch	682.36 (116.05) *.98*	683.07 (150.04) *.79*
		Non-congruent	Switch	906.31 (184.72) *.52*	929.50 (260.60) *.37*
			No-switch	868.32 (172.02) *.94*	901.14 (241.81) *.71*
	Location	Congruent	Switch	731.84 (148.08) *.59*	723.13 (196.83) *.49*
			No-switch	682.01 (133.95) *.97*	668.64 (162.60) *.82*
		Non-congruent	Switch	842.06 (148.95) *.47*	943.24 (285.11) *.38*
			No-switch	782.72 (134.70) *.81*	811.75 (160.94) *.74*

Table 2a describes the significant switch-related activation demonstrated by the TD group. The switching – non-switching blocks contrast map was thresholded using clusters determined by Z > 2.3, which is equivalent to a corrected cluster significance threshold of p < .05. This map was divided into clusters of activity that were associated with a switch-related contrast Z-score greater than 3.0 and comprised more than 100 voxels, ensuring that, as far as possible, the described clusters did not span regions that are known to be functionally dissociable.

Brain region	**Hemisphere**	**MNI coordinates of maximum activity**			**Cluster size (voxels)**	**TD group: Z value for switch-related activation**
		x	**y**	**z**		
Superior lateral occipital cortex	L	-10	-80	50	573	4.23
	L	-19	-69	41	159	3.62
	R	13	-74	45	494	4.13
Posterior supramarginal gyrus	L	-49	-42	49	1766	5.64
Paracingulate gyrus /anterior cingulate	B	11	16	45	1560	4.54
	R	5	32	33	252	5.03
Inferior frontal gyrus	L	-47	14	19	444	5.41
Frontal pole/ middle frontal gyrus	L	-39	43	18	1163	5.90
Frontal pole	L	-41	54	11	127	4.65
	L	-29	51	0	150	3.92

Table 2b describes the significant switch-related deactivation demonstrated by the TD group. The non-switching – switching blocks contrast map was thresholded using clusters determined by Z > 2.3, which is equivalent to a corrected cluster significance threshold of p < .05. This map was divided into clusters of activity that were associated with a switch-related contrast Z-score greater than 3.0 and comprised more than 100 voxels, ensuring that, as far as possible, the described clusters did not span regions that are known to be functionally dissociable.

Brain region	**Hemisphere**	**MNI coordinates of maximum activity**			**Cluster size (voxels)**	**TD group: Z value for switch-related activation**
		x	**y**	**z**		
Medial frontal cortex / frontal pole	R	2	50	-8	217	3.84
Superior frontal gyrus/ frontal pole	L	-2	58	27	548	4.03
	L	-10	59	17	134	4.39
Paracingulate gyrus	L	-7	49	7	133	4.05
Frontal pole, superior	B	-3	66	7	472	5.04
	L	-17	67	5	140	3.76
Frontal pole, inferior	B	-16	59	-17	532	4.82
	L	-13	66	-6	113	4.11

Table 3 describes the significant switch-related activation demonstrated by the PWS group. The switching – non-switching blocks contrast map was thresholded using clusters determined by Z > 2.3, which is equivalent to a corrected cluster significance threshold of p < . This map was divided into clusters of activity that were associated with a switch-related contrast Z-score greater than 3.0 and comprised more than 100 voxels, ensuring that, as far as possible, the described clusters did not span regions that are known to be functionally dissociable.

Brain region	**Hemisphere**	**MNI coordinates of maximum activity**			**Cluster size (voxels)**	**PWS group: Z value for switch-related activation**
		x	**y**	**z**		
Cuneus / precuneus / superior lateral occipital cortex	L	-1	-86	41	1286	5.47
Superior lateral occipital cortex	R	25	-77	46	285	4.24
	R	10	-82	41	230	4.39
Cuneal cortex/ precuneus	L	-18	-71	24	219	4.42

Table 4 describes the areas in which the switching – non-switching blocks activity was significantly greater in the TD relative to the PWS participants. The TD – PWS switch-related activation contrast map was thresholded using clusters determined by $Z > 2.3$, which is equivalent to a corrected cluster significance threshold of $p < .05$. This map was divided into clusters of activity that were associated with a TD – PWS contrast Z-score greater than 3.0 and comprised more than 50 voxels. Mean percentage signal change values associated with switching and non-switching block wave forms were extracted from the mean activity across the four scans for each participant using FEATquery.

Brain region	**Hemisphere**	**MNI coordinates of maximum activity**			**Cluster size (voxels)**	**Z value for switch-related activation in TD *minus* PWS group**	**Control group**	**PWS group**
		x	**y**	**z**			**Mean (SD) % signal change in non-switch – switch blocks**	**Mean (SD) % signal change in non-switch – switch blocks**
Hippocampus/ brain stem	B	-2	-16	-16	1087	4.38	.16 (.14) $t(7)=2.47$, $p= .043$	-.20 (.18) $t(7)=-3.06$, $p= .018$
Putamen/ amygdala/ hippocampus	L	-23	-11	-11	347	3.88	.10 (.06) $t(7)=4.06$, $p= .005$	-.21 (.13) $t(7)=-3.36$, $p= .012$
Thalamus	R	15	-4	11	89	3.6	.07 (.15) $t(7)=1.28$, $p= .242$	-.14 (.21) $t(7)=-3.16$, $p= .016$
Middle frontal gyrus/ sub gyral white matter/ insula	L	-27	-4	26	629	4.21	.11 (.11) $t(7)=2.60$, $p= .036$	-.16 (.17) $t(7)=-2.50$, $p= .041$
Right middle frontal gyrus/ insula	R	30	24	17	533	4.03	.20 (.21) $t(7)=2.91$, $p= .022$	-.12 (.14) $t(7)=-2.34$, $p= .052$
Inferior frontal gyrus	R	38	13	20	181	4.00	.18 (.20) $t(7)=2.40$, $p= .047$	-.11 (.18) $t(7)=-1.84$, $p= .108$
Precentral gyrus/ sub gyral white matter	L	-32	-14	44	458	3.90	.08 (.09) $t(7)=3.10$, $p= .017$	-.14 (.13) $t(7)=-3.04$, $p= .019$
Posterior supramarginal gyrus	L	-37	-52	18	285	3.76	.12 (.13) $t(7)=2.35$, $p= .051$	-.06 (.12) $t(7)=-1.53$, $p= .169$
	L	-57	-44	12	141	3.71	.12 (.09) $t(7)=2.55$, $p= .038$	-.13 (.14) $t(7)=-2.62$, $p= .035$
Middle/ posterior temporal gyrus	L	-48	-44	-10	270	3.69	.10 (.11) $t(7)=2.18$, $p= .065$	-.16 (.17) $t(7)=-2.69$, $p= .031$

Table 5 describes the areas in which the switching – non-switching blocks activity was significantly greater in the PWS relative to the TD participants. The PWS – TD switch-related activation contrast map was thresholded using clusters determined by $Z > 2.3$, which is equivalent to a corrected cluster significance threshold of $p < .05$. This map was divided into clusters of activity that were associated with a PWS – TD contrast Z-score greater than 3.0 and comprised more than 50 voxels. Mean percentage signal change values associated with switching and non-switching block wave forms were extracted from the mean activity across the four scans for each participant using FEATquery.

Brain region	**Hemisphere**	**MNI coordinates of maximum activity**			**Cluster size (voxels)**	**Z value for switch-related activation in PWS *minus* TD group**	**Control group**	**PWS group**
		x	**y**	**z**			**Mean (SD) % signal change in non-switch – switch blocks**	**Mean (SD) % signal change in non-switch – switch blocks**
Inferior, anterior frontal pole	L	-18	65	-16	554	4.77	-.21 (.17) $t(7)=-3.09$, $p= .018$	.21 (.19) $t(7)=4.23$, $p= .004$
	R	9	62	-17	467	4.05	-.24 (.22) $t(7)=-3.26$, $p= .014$	.18 (.34) $t(7)=1.50$, $p= .177$

Table 6 describes the pairs of PWS and TD participants matched for chronological age and gender.

Pair	Gender	Age (years: months)	
		PWS participant	**TD participant**
1	M	40: 4	40:0
2	M	24:10	21:0
3	F	18:4	16:9
4	M	16:2	17:8
5	M	11:3	12:5
6	F	16:2	14:9
7	M	14:9	16:2
8	F	26:8	25:11

FIGURE CAPTIONS

Figures 1 and 2 show four rows of images that each depict the brain from a different view point, all with an elevation of 0°. From top to bottom row 1 shows azimuth 270° (viewed from the left of the person), row 2 azimuth 0° (viewed from the back), row 3 azimuth of 90° (viewed from the right) and row 4 azimuth 180° (viewed from the front). The three columns each show different proportions of the brain. From the left column 1 shows the whole brain, column 2 shows 80% and column 3 shows 70% of the brain, sectioned along a plane perpendicular to the viewing angle.

Figure 1 shows the switching – non-switching and non-switching – switching blocks contrasts in the TD group. Switch-related neural activation is shown in red and switch-related deactivation is shown in blue.

Figure 2 shows the switching – non-switching and non-switching – switching blocks contrasts in the PWS group. Switch-related neural activation is shown in red and switch-related deactivation is shown in blue.

Figure 3 shows the contrast between TD and PWS groups for the switching – non-switching blocks contrast. Regions where switching-block – non-switching block activity is significantly greater in the TD group relative to the PWS group are shown in violet and regions where this activity is significantly greater in the PWS group relative to the TD group are shown in green. The four rows of images each depict the brain from a different view point, equal to those in Figures 1 and 2. From left to right, row 1 shows 80%, 70% and 60% of the brain sectioned along a plane perpendicular to the viewing angle; row 2 shows 80%, 70% and 50% sections; row 3 shows 100%, 80% and 60% sections and row 4 shows 100%, 80% and 50% sections.

Figure 4 illustrates the fMRI task stimuli presented to PWS participants and the experimental procedure that was followed within switching blocks. Sizes of stimuli are given in degrees of the visual angle, colours are described in RGB intensity values.

Figure 5 illustrates the fMRI task stimuli presented to PWS participants and the experimental procedure that was followed within non-switching identity task blocks. Sizes of stimuli are given in degrees of the visual angle, colours are described in RGB intensity values.

Figure 6 illustrates the fMRI task stimuli presented to TD participants and the experimental procedure that was followed within non-switching location task blocks. Sizes of stimuli are given in degrees of the visual angle, colours are described in RGB intensity values.

Figure 1

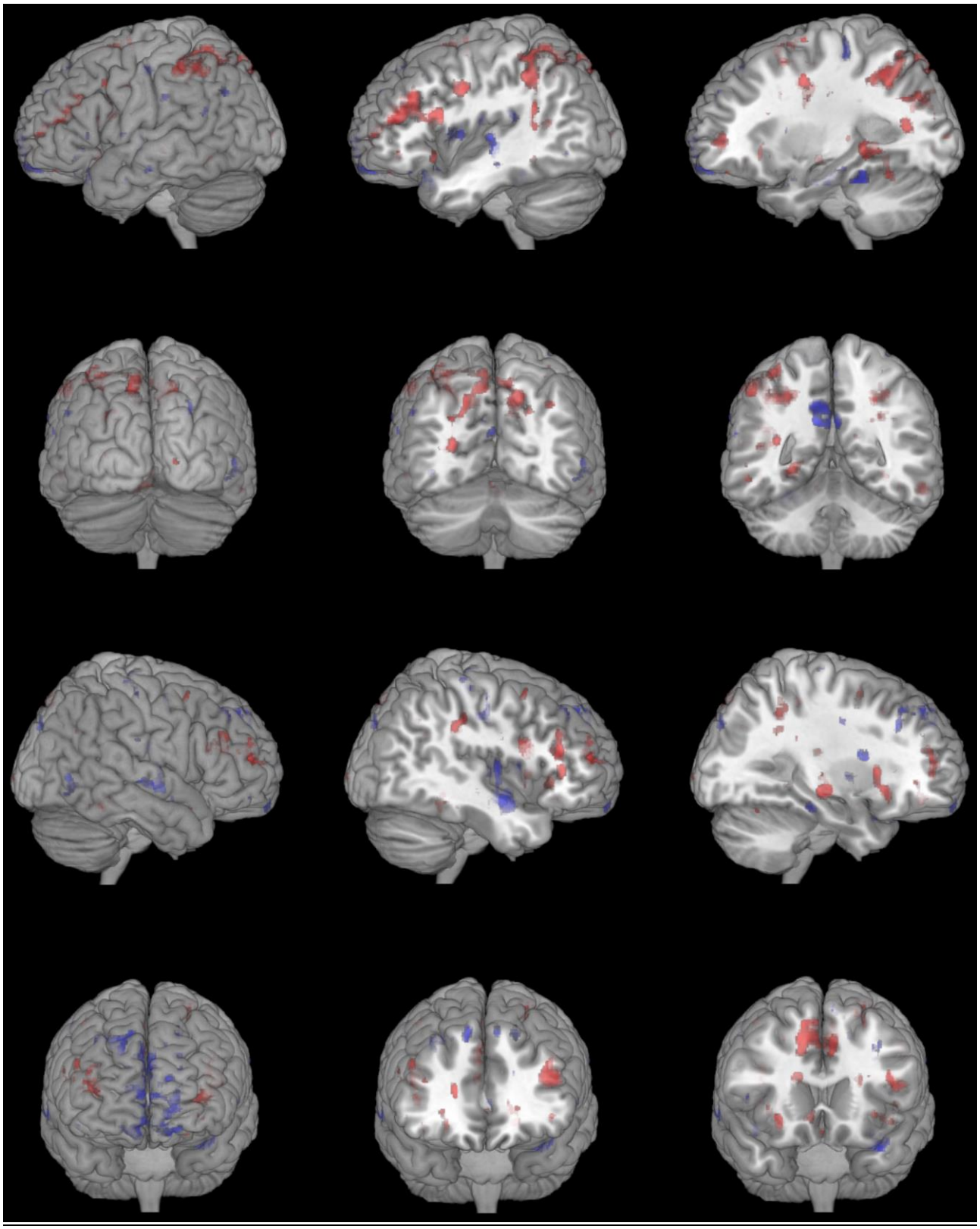

Figure 2

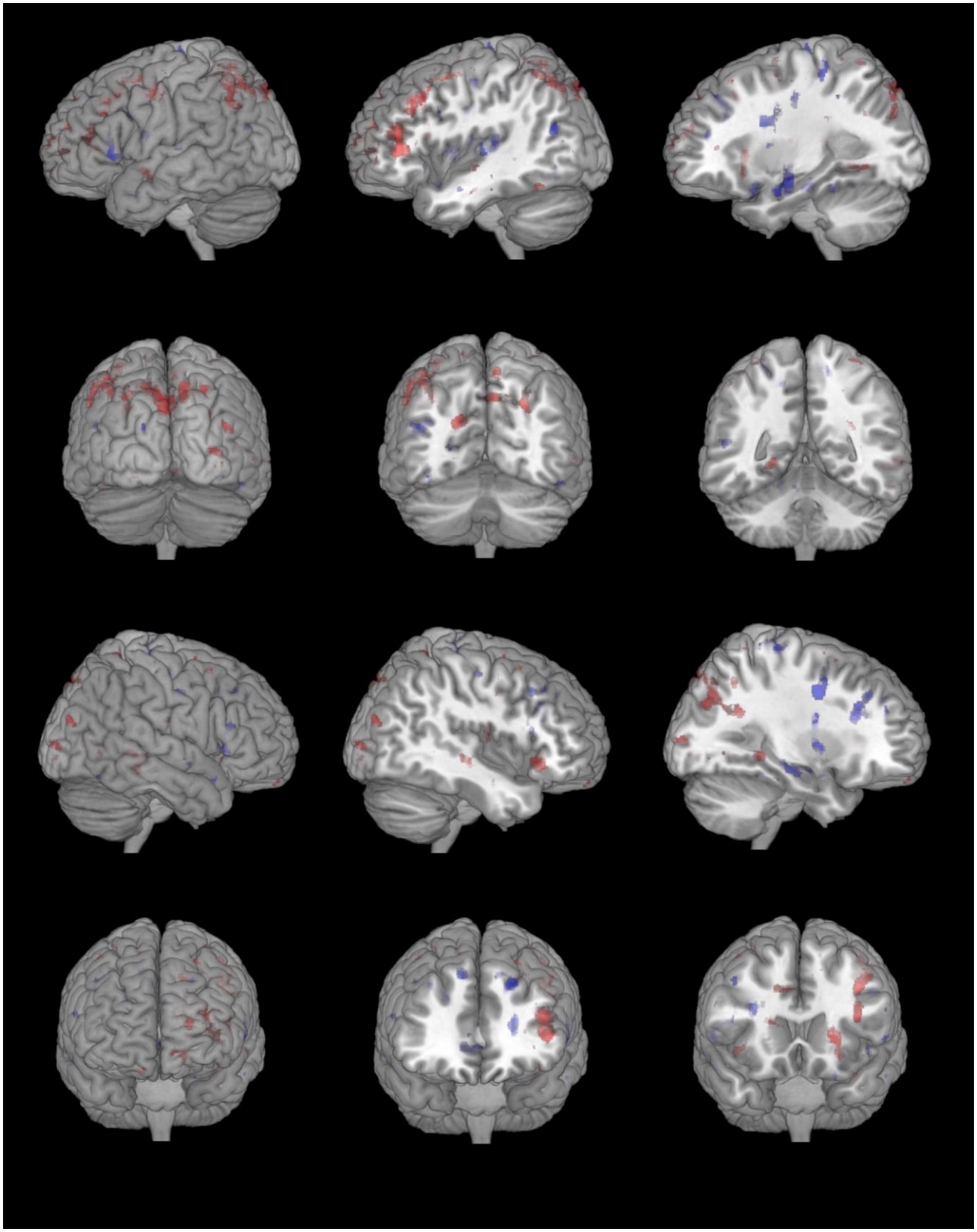

Figure 3

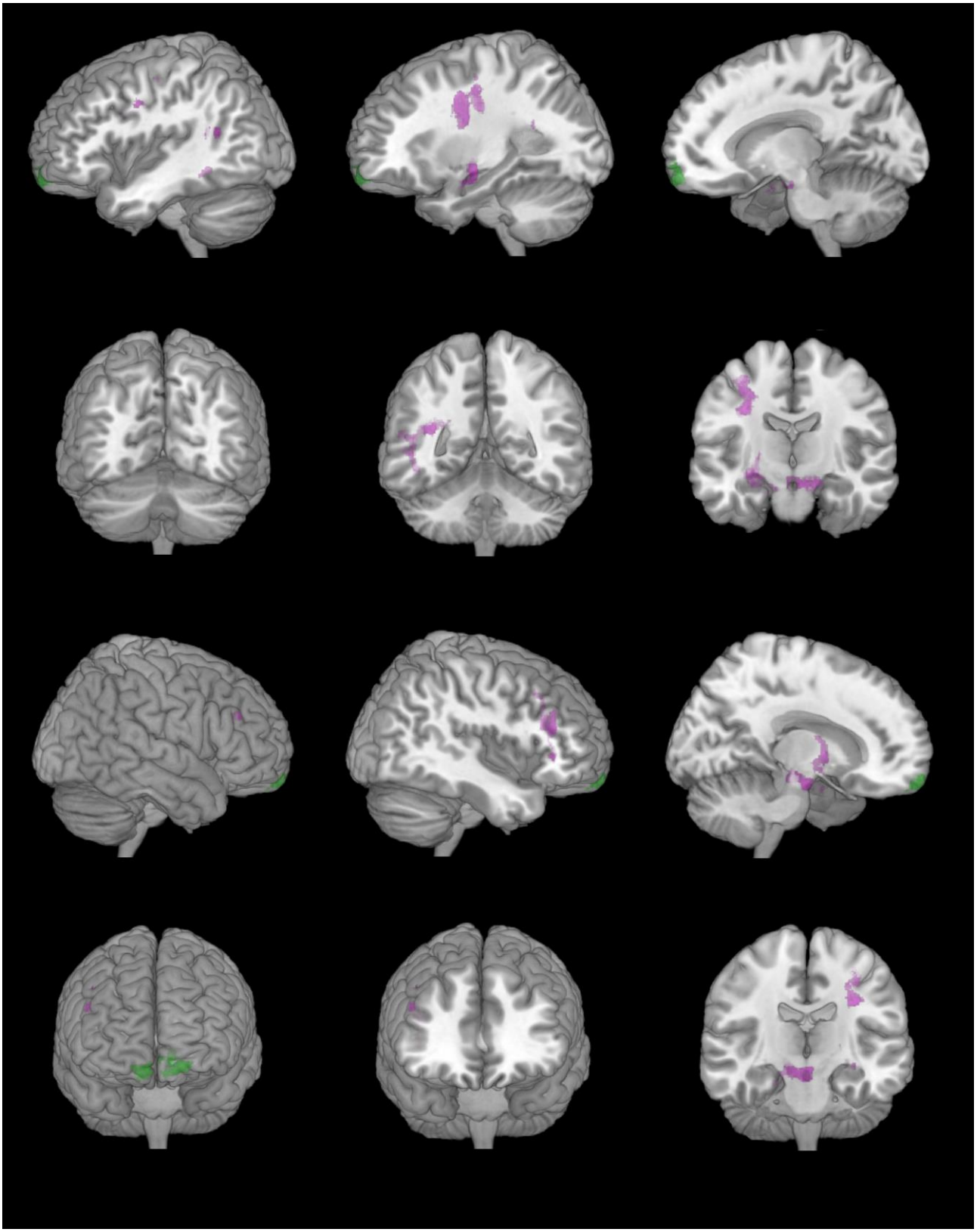

Figure 4

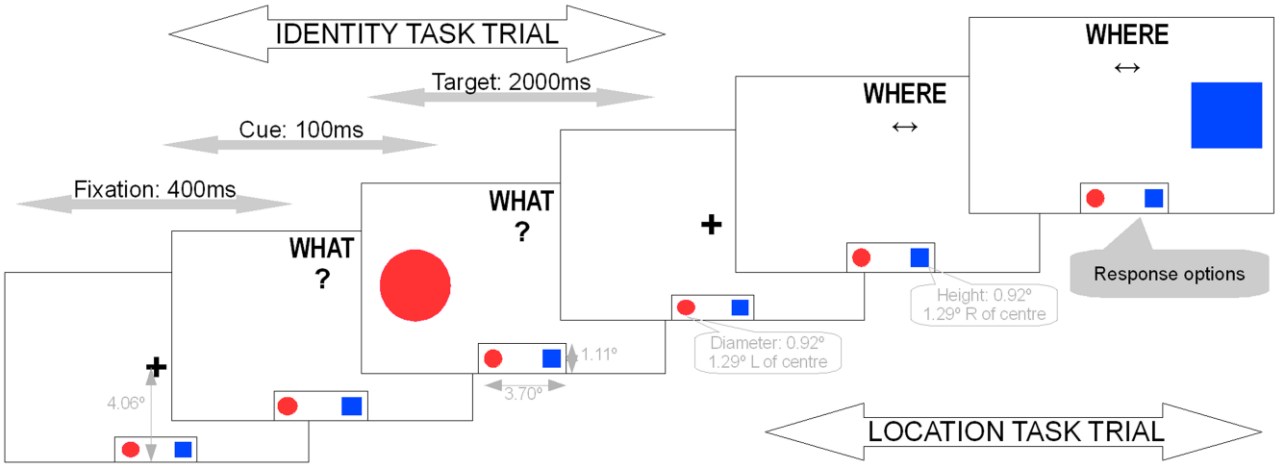

Figure 5

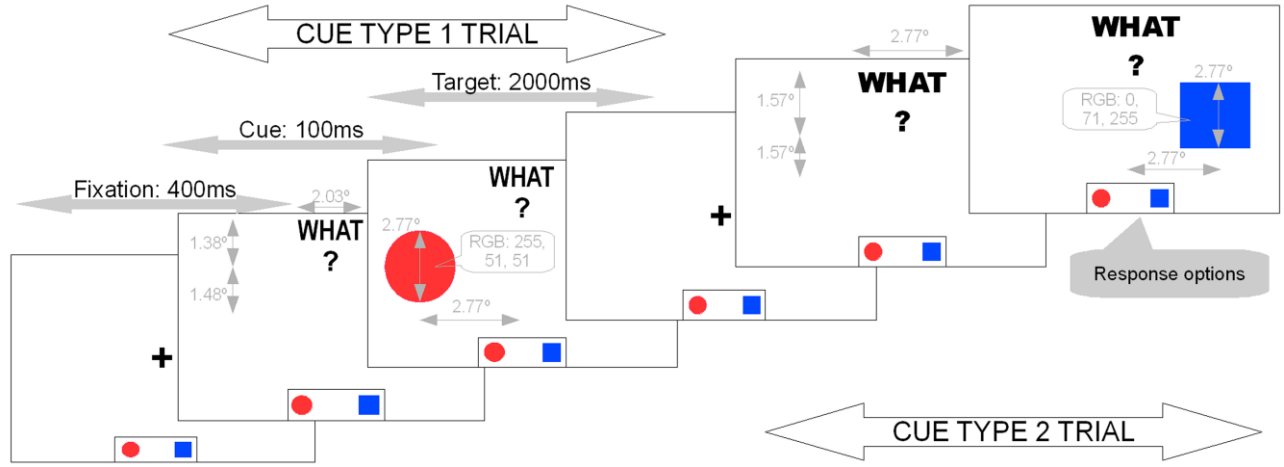

Figure 6