

Frontostriatal Dysfunction During Response Inhibition in Williams Syndrome

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Background: Williams syndrome (WS) has provided researchers with an exciting opportunity to understand the complex interplay among genes, neurobiological and cognitive functions. However, despite a well-characterized cognitive and behavioral phenotype, little attention has been paid to the marked deficits in social and behavioral inhibition. Here we explore the neural systems that mediate response inhibition in WS.

Methods: We used functional MRI (fMRI) to obtain blood oxygenation level dependence (BOLD) signal maps during the performance of a Go/NoGo response inhibition task from 11 clinically and genetically diagnosed WS patients and 11 age- and gender-matched typically developing (TD) control subjects. Correlations between behavioral, neuropsychological measures, and BOLD signal were also conducted.

Results: Although TD control subjects showed significantly faster response times, no group differences in behavioral accuracy were observed. Compared with control subjects, WS participants demonstrated significantly reduced activity in the striatum, dorsolateral prefrontal, and dorsal anterior cingulate cortices. These findings support the hypothesis that persons with WS fail to activate critical cortical and subcortical structures involved in behavioral inhibition.

Conclusions: Our results provide important evidence for reduced engagement of the frontostriatal circuits in WS and provide putative biological markers for the deficits in response inhibition and the unusual social phenotype.

Key Words: fMRI, Go/NoGo, prefrontal cortex, response inhibition, striatum, Williams syndrome

Williams syndrome (WS) is a lifelong neurodevelopmental condition associated with a contiguous 1.6-microdeletion on the long arm of chromosome 7q11.23 (Ewart *et al.* 1993; Korenberg *et al.* 2000). In parallel to an increasingly well-defined genetic profile, a recent surge of neuroimaging and histological studies have begun to demonstrate a consistent neuroanatomic phenotype that maps directly onto the WS neuropsychological profile (Galaburda and Bellugi 2000; Kippenhan *et al.* 2005; Reiss *et al.* 2004; Thompson *et al.* 2005). For example, it is widely believed that atypical development of the dorsal “where” pathway, which extends over the superior occipital and parietal cortices, underlies conspicuous impairments in visuospatial constructive abilities (Atkinson *et al.* 2003; Bellugi *et al.* 2000; Mervis *et al.* 2000). By contrast, the relatively proficient verbal performance and expressive language typically associated in this syndrome is thought to arise from the relative preservation of the ventral “what” pathway, which encompasses the inferior portions of the occipital and temporal cortices (Bellugi *et al.* 2000; Meyer-Lindenberg *et al.* 2004; Mobbs *et al.* 2004).

Beyond these peaks and valleys in cognition, individuals with

WS frequently display problems with suppression of inappropriate behaviors. For example, despite being able to discriminate between the approachability and nonapproachability of faces, individuals with WS have difficulty suppressing the urge to interact socially (Frigerio *et al.* 2006). Although this characteristic of the WS behavioral phenotype is particularly evident during social discourse (Jones *et al.* 2000), problems with inhibition extend across many facets of daily functioning. Although relatively little attention has been paid to these deficits in WS, the broader manifestations of inhibition deficits often include inattention, distractibility, low frustration tolerance, and diminished stranger anxiety (Tomc *et al.* 1990). Not surprisingly, individuals with WS often meet the diagnostic criteria for comorbid attention-deficit/hyperactive-disorder (ADHD; Carrasco *et al.* 2005). As a consequence, deficits in inhibition may result in marked disruption to academic attainment, social relationships, and vocational pursuits (Einfield *et al.* 1997; Howlin and Udwin 2006).

The neurobiological systems that subserve response inhibition and executive functions have been extensively investigated in nonhuman primates (Iversen and Mishkin 1970; Minaminmoto *et al.* 2005), in typically developing (TD) human subjects using functional imaging (Garavan *et al.* 2000; Menon *et al.* 2001), and in patients with acquired lesions (Aron *et al.* 2004). Collectively, these studies point to a network of interconnected cortical regions that underlie this critical cognitive function including the dorsolateral prefrontal cortex (dlPFC), right inferior frontal gyrus (IFG), and dorsal anterior cingulate cortex (dACC). Recent studies have also demonstrated an important role for the striatum in behavioral inhibition, particularly in relation to the pathogenesis of neurodevelopmental disorders such as ADHD (Aron *et al.* 2004; Monchi *et al.* 2006) and fragile X (Menon *et al.* 2004). Recruitment of these regions may reflect their high density of noradrenalin and dopaminergic synapses, neurotransmitters thought to be important in the regulation of behavioral inhibition (Aron and Poldrack 2005; Chamberlain *et al.* 2006). Despite a well-characterized network in TD subjects, it still remains largely

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unknown whether any of these regions are disrupted in WS and therefore contribute to the adaptive behavioral problems shown by this population.

This functional magnetic resonance imaging (fMRI) study was designed to explore the neurobiological systems that underlie response inhibition and attentional deficits in WS using the classic Go/NoGo paradigm, a simple task that requires a blend of neurocognitive components including target recognition, prolonged attention, and rule maintenance (Aron and Poldrack 2005; Menon *et al.* 2004). Based on results from previous structural and functional imaging experiments in our laboratory and others (Meyer-Lindenberg *et al.* 2004; Mobbs *et al.* 2004; Reiss *et al.* 2004; Thompson *et al.* 2005) and given the connectivity of the dorsal-stream posteriorly to numerous zones of the PFC (Atkinson *et al.* 2003), we hypothesized that the biological origins of inhibition deficits in WS stem from anomalous engagement of several prefrontal regions including the dlPFC and dACC. However, we expected the vlPFC and right IFG to be less disrupted because these may be modulated by ventral-stream input. A last key prediction was that these frontal deficits would be accompanied by aberrant modulation of striatal structures (i.e., caudate and putamen) associated with behavioral and social inhibition (Meyer-Lindenberg *et al.* 2005; Reiss *et al.* 2004).

Methods and Materials

Participants

Eighteen individuals with WS were recruited. Seven of these participants were later excluded from the study for below-chance performance and excessive head motion (> 3 mm). The remaining group consisted of 11 participants (9 female subjects) with a mean age (\pm SD) of 31.4.0 (\pm 12.1) years; range 15.5–48.8). Genetic diagnosis was established using fluorescence in situ hybridization (FISH) probes for elastin (*ELN*), a gene consistently found in the microdeletion associated with WS (Ewart *et al.* 1993; Korenberg *et al.* 2000). In addition, all participants exhibited the medical and clinical features of the WS phenotype, including cognitive, behavioral, and physical profiles (Bellugi *et al.* 2000).

The TD adult control subjects consisted of 11 healthy participants (9 female participants; mean age 30.2 \pm 11.1; range 19.4–54.6), matched for chronological age. Each participant was deemed asymptomatic as determined by screening for current or past history of psychiatric or neurologic problems and using the Symptom Checklist-90-R (SCL-90-R; Derogatis 1977). For all participants, cognitive functioning was assessed using the Wechsler Intelligence Scale for Children, Revised (3rd ed.; WISC-III) for those aged under 16 years. For ages 16 and up, the Wechsler Adult Intelligence Scale (3rd ed.; WAIS-III) was used. Both the WAIS-III and WISC-III assessed Verbal IQ (VIQ), Performance IQ (PIQ), and Full-Scale IQ (FSIQ). In addition, all participants were native English speakers, reported being right-handedness (confirmed using the Edinburgh Handedness Scale; Oldfield 1971), and gave written informed consent before participation. All experimental procedures complied with the standards of the human subjects committee at Stanford University School of Medicine.

Experimental Paradigm

Before the scan, all subjects completed a practice version of the task. Research staff ensured that all subjects were capable of attending to and performing the tasks in the scanner. The experimental task consisted of a 30-sec rest epoch, 12 alternating 26-sec epochs of Go and Go/NoGo conditions, followed by a

30-sec rest epoch. During both conditions, letters were presented every 2 sec. In the Go/NoGo condition, subjects responded with a key press to every letter except X (presented on 50% of the trials) to which they were instructed to withhold response. In the Go condition, subjects responded with a button press to every letter (no Xs were presented). At the beginning of each epoch, a 2-sec instruction alerted the subject to the new task condition (Figure 1A). Errors of omission, commission, and response time (RT) to correct trials during the experimental condition were recorded. Stimuli were presented visually at the center of a screen using a custom-built magnet compatible projection system (Resonance Technology, Northridge, California). Stimuli were presented using Psychscope (Cohan 1993).

fMRI Parameters

Images were acquired on a 1.5-T GE Signa scanner with Echospeed gradients using a custom-built whole-head coil that provides a 50% advantage in signal-to-noise ratio over that of the standard GE coil. A custom-built headholder was used to prevent head movement. Eighteen axial slices (6 mm thick, 1 mm skip) parallel to the plane containing the anterior and posterior commissures covering the whole brain were imaged with a temporal resolution of 2 sec using a T2* weighted gradient echo spiral pulse sequence (repetition time = 2000 msec, echo time = 40 msec, flip angle = 89°, and 1 interleave). The field of vision was 240 mm and the effective in-plane spatial resolution was 4.35

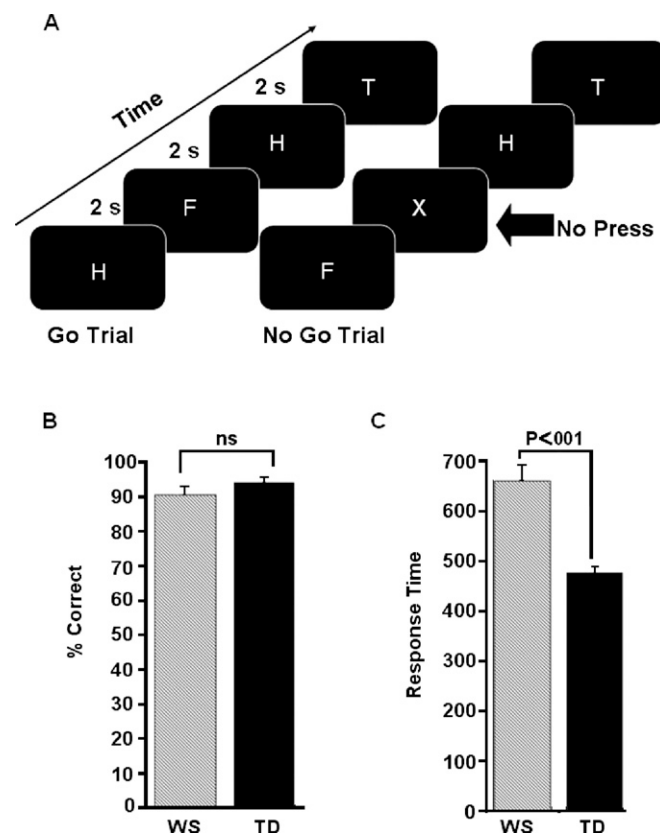


Figure 1. (A) Schematic diagram of the Go/NoGo paradigm. During the Go (control) block, subjects were asked to press a button each time a letter appeared. In the experimental Go/NoGo block, subjects were asked to press for every letter except the letter X. Twenty-four alternating Go and NoGo blocks were presented, with each block lasting 26 secs. Blocks were interleaved with 30-sec rest epochs. (B) Percent correct and SEM for NoGo trials. (C) Response times for NoGo Trials. *ns*, not significant.

mm. To aid in the localization of functional data, a high-resolution T1-weighted structural image was acquired.

Image Processing and Statistical Analysis

Images were reconstructed, by inverse Fourier transform, for each of the 186 time points into $64 \times 64 \times 18$ image matrices (voxel size: $3.75 \times 3.75 \times 7$ mm). The fMRI data were preprocessed using SPM99 (<http://www.fil.ion.ucl.ac.uk/spm>). Briefly, images were corrected for movement, normalized to stereotaxic Talairach coordinates, and smoothed with a 4-mm Gaussian kernel to decrease spatial noise. Following preprocessing, statistical analysis was performed on individual and group data using the general linear model and the theory of Gaussian random fields as implemented in SPM99. A within-subject procedure was first used to model all of the effects of interest for each subject. Confounding effects of fluctuations in global mean were removed by proportional scaling in which, for each time point, each voxel was scaled by the global mean at that time point. Low-frequency noise was removed with a high-pass filter (.5 cycles per min) applied to the fMRI time series at each voxel. A temporal smoothing function (Gaussian kernel corresponding to dispersion of 8 sec) was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. We defined the effects of interest for each subject with the relevant contrasts of the parameter estimates. For each of these contrasts, a corresponding contrast image was also created.

Group analysis was performed using a random-effects model in a two-stage hierarchical procedure. The aim of this analysis was to determine which brain regions showed significant activation for each main effect and interaction of interest. Initially, we computed a contrast image corresponding to the Go/NoGo versus Go condition for each subject. We then used these contrast images to compute (*i*) within-group (TD control subjects and WS) and (*ii*) between-group activations using one- and two-sample, voxel-wise, *t* tests, respectively. The *t* statistics were then normalized to *Z* scores, and significant clusters of activation were determined using the joint expected probability distribution of height and extent of *Z* scores, with height ($Z > 1.96$; $p < .05$) and extent threshold ($p < .05$: whole-brain corrected). Further details of methods can be found elsewhere (Menon *et al.* 2004).

Results

IQ

FSIQ scores for the WS group (mean \pm SD 69.8 ± 10.1 ; range 39–80) were significantly lower than TD control subjects (117.7 ± 13.9 ; range 99–130; $p < .0001$). Verbal and performance IQ scores followed a similar pattern for both the WS group (VIQ = 64.5 ± 10.3 , range 49–89; PIQ = 65.2 ± 11.2 , range 44–79) and TD group (VIQ = 110.6 ± 17.6 , range 86–132; PIQ = 121.2 ± 8.9 , range 65–125; two-tailed *t* test; $p < .0001$).

Response Times and Accuracy

Analysis of the behavioral data for the Go/NoGo condition showed no statistical differences for accuracy between WS and

Table 1. Behavioral Performance for Go and Go/No Go Trials

Condition	Subject Group	Accuracy	Response Time
Go	TD	$99.7 \pm .1$	393.2 ± 80.7
	WS	89.2 ± 17.7	571.9 ± 177.5
No Go	TD	94.0 ± 5.76	475.9 ± 47.7
	WS	90.5 ± 8.2	661.0 ± 100.5

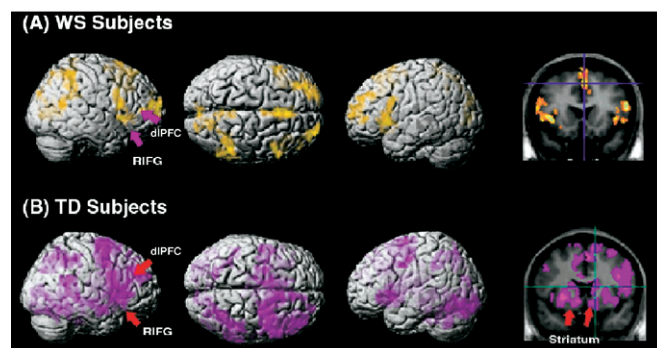


Figure 2. Surface renderings and selected slices showing significant loci of activation for (A) individuals with Williams syndrome (WS) and (B) typically developing control subjects for the Go/NoGo minus Go contrast. Note the lack of significant activity in the striatum, dorsolateral prefrontal cortex, and cerebellum in subjects with WS.

TD subjects (Mann–Whitney $Z = -.798$ $p < .425$; Figure 1B). Statistical differences were found between WS and TD control subjects for response times (RT; Mann–Whitney $Z = -3.64$ $p < .001$; Figure 1C; Table 1). A significant positive correlation between accuracy and RT was observed for both the WS (Spearman's $r = .658$; two-tailed $p < .028$) and the TD groups (Spearman's $r = .645$; two-tailed $P < .032$). Furthermore, negative correlations between FSIQ and accuracy were observed in both the WS (Spearman's $r = -.703$; $p < .016$) and TD groups (Spearman's $r = -.661$; $p < .027$). See Table 1.

Brain Imaging Results

Within-Group Activations In our initial analyses, neural activity during the NoGo blocks of stimuli were compared with activity during the “Go” blocks (Figure 1A). A WS within-group analysis revealed increased activation in the right superior parietal gyrus (Brodmann's area [BA] 7; $Z = 3.26$, 323 voxels; MNI = 8, -42, 76) and supramarginal gyrus (BA 40; $Z = 3.72$, 738 voxels; 56, -42, 36), cuneus (BA 23; $Z = 3.25$, 759 voxels; 12, -72, 8), right IFG (BA 47/44; $Z = 3.55$, 591 voxels; 46, 10, 28), and middle frontal gyrus (MFG; BA46; $Z = 3.59$, 346 voxels; 28, 62, 6) extending to the superior frontal gyrus (BA 44/9; $Z = 4.07$, 823 voxels; 4, 24, 54). Within the left hemisphere, the WS group showed activation in the anterior insula extending to the IFG (BA 44; $Z = 3.62$, 683 voxels; -40, 18, 0), MFG (BA 46), paracingulate/medial frontal gyrus (Mfd) extending to dACC (BA 32/9; $Z = 3.40$, 668 voxels; -30, 42, 76). The TD within-group analysis showed significant activation in the right MFG extending to the IFG, dlPFC, supplementary motor area (SMA), and dACC (BA 46/44/8/32; $Z = 4.29$, 7030 voxels; 40, 2, 66). Clusters were also observed in the inferior parietal lobule (IPL; BA 7; $Z = 2.97$, 614 voxels; -18, -68, 46), extending to the right postcentral gyrus (BA1/2) and the left insula (BA 13; $Z = 5.06$, 14974 voxels; -40, 14, 0) extending to the striatum and IFG (BA 44/45). A final cluster was observed in the right IPL (BA 40/7, 1515 voxels; 46, -31, 46) extending to the superior parietal lobule and precuneus (BA 7). No significant correlations between RT, FSIQ and BOLD signal were found in the WS group ($p < .05$ corrected). Similarly, TD control subjects showed no correlations between FSIQ and BOLD signal. However, TD control subjects did demonstrate decreases in RT that correlated with BOLD signal in the posterior Mfd and cingulate gyrus (BA 6/24/31; $p < .001$; $Z = 3.94$; -2, -14, 72) (Figure 2).

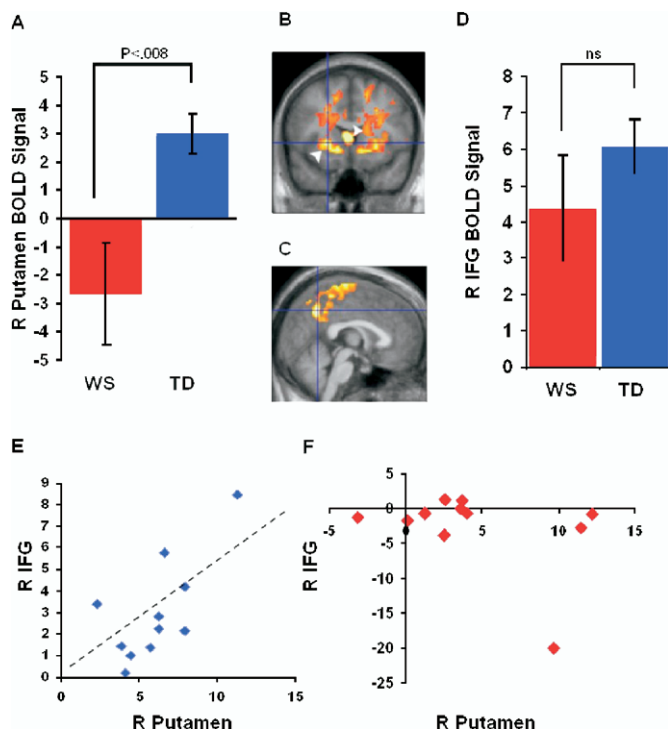


Figure 3. (A) Bar graph and SEM for the comparison of right putamen (22, 12, 2:8 mm sphere) parameter estimates for Williams syndrome (WS) and typically developing (TD) control subjects (two-tailed independent t test: $t_{20} = -2.931$; $p < .008$). (B) Statistical parametric map (SPM) showing those regions that were more active in TD control subjects than WS subjects. The arrows point to the putamen and caudate. (C) SPM map illustrating increased posterior cingulate and precuneus activation for the WS group–TD group comparison. (D) Bar graph and SEM showing no between group differences between activity in the right inferior frontal gyrus (IFG; Peak [8-mm sphere]: 52, 24, 6; $t_{20} = -1.05$; $p < .305$). (E) The TD control subjects showed a positive correlation between right putamen and right IFG activity (Pearson's $r = .712$; $p < .014$, two-tailed). (F) No correlation was found between the right IFG and right putamen for the WS group (Pearson's $r = -.381$; $p < .247$, two-tailed).

Between-Group Comparisons The WS group, when compared with the control group, showed increased activation in the medial precuneus extending to the posterior cingulate cortex (PCC; BA 7/31; $Z = 4.04$, 1560 voxels; 0, -56, 42). By comparison, the TD group showed greater activation in the bilateral striatum, peaking in the left putamen and extending to several cortical regions including the right superior frontal gyrus, bilateral dACC, right frontal middle gyrus, dlPFC, and bilateral middle temporal gyrus (BA 6/9; $Z = 4.55$, 23,432 voxels; -22, 12, 2; Figure 3).

Discussion

This study was designed to examine the neural systems underlying response inhibition and attention in WS using a well-established Go/NoGo paradigm. Despite significantly lower IQs, WS subjects showed task accuracy comparable to the TD group, although RT was significantly slower in the WS group. A positive correlation between accuracy and increased RT suggested that both WS and TD subjects used a RT–accuracy trade-off strategy. Analysis of fMRI data showed both WS and TD groups activated the bilateral IFG. Both within and between-group statistical comparisons, however, revealed relatively reduced activation in the dlPFC, dACC and striatum in the WS group compared to controls. These findings suggest that inhibi-

tion problems in WS stem from failure to recruit frontostriatal circuits implicated in behavioral inhibition. Furthermore, WS subjects showed anomalous activity in the PCC and precuneus, regions previously implicated in response inhibition failure in ADHD (Rubia *et al.* 2005). No correlations among RT, IQ, and BOLD signal were found within the WS group, supporting the claim that activation differences result from the syndrome rather than differences in IQ or performance.

Reduced engagement of the striatum in WS is compelling given its putative role in the pathogenesis of numerous disorders of volition including ADHD (Castellanos *et al.* 2002), obsessive-compulsive disorder (van den Heuvel *et al.* 2005a, 2005b), and fragile X syndrome (Menon *et al.* 2004). In TD subjects, reduced striatal activity has been associated with response inhibition failure (Vink *et al.* 2005). More constrained analysis by Monchi and colleagues (2006) supports the claim that whereas the putamen is involved in execution of action, the caudate is more involved in planning. The striatum is thought to play a crucial role in many aspects of frontal function providing output via a striatal–thalamocortical loop to regions important in behavioral inhibition including the ACC, orbital, and lateral prefrontal areas (Alexander 1986; Middleton 2000, 2002). A recent DTI study showed that stronger frontostriatal connectivity is associated with faster response time on Go/NoGo task (Liston *et al.* 2006), thus supporting the notion that WS, who also had decreased RT, have disruptions to this circuit. Although no microanatomic studies of the WS striatum exist, clues that this structure is abnormal come from a recent voxel-based morphometry study in which gray matter within the caudate body was observed to be reduced (Reiss *et al.* 2004), a finding that mirrors those observed in children with ADHD (Castellanos *et al.* 2002). Interestingly, recent imaging studies have begun to implicate the striatum in guiding social behavior including trust, which is known to be overstated in WS (Frigerio *et al.* 2006; Jones *et al.* 2000; King-Casas *et al.* 2005). Given that frontostriatal circuits are implicated in social and cognitive operations, further imaging and postmortem histological studies in WS aimed at elucidating structure–function relationships in this neural circuit are warranted.

Several lines of evidence from primate to human neurophysiologic studies support the notion that the right IFG is critical to behavioral inhibition (Aron *et al.* 2004). The right IFG is a core node in the inhibition network and acquired lesions to this region cause dramatic deficits in behavioral inhibition (Aron *et al.* 2003a, 2003b). Both the WS and TD control group showed increased activation in the right IFG. This suggests that the right IFG is modulated at a level equal to that of the TD control subjects. Although no previous fMRI studies targeting this region in WS have been conducted, structural imaging studies have shown the right prefrontal region to have gyrification and cortical thickness indices in the normal range (Kippenhan *et al.* 2005; Schmitt *et al.* 2002; Thompson *et al.* 2005). Importantly, the right IFG receives direct input from the striatum (Middleton *et al.* 2000). As well, BOLD signal may reflect input into, rather than output from, particular brain regions (Logothetis *et al.* 2001). Thus, aberrant striatal input might also contribute to disrupted frontal cortical functioning. This might be most prominent during social and emotional inhibition (Frigerio *et al.* 2006; Shafritz *et al.* 2006). With this question in mind, we examined the relationship between BOLD signal in the peak right striatum (i.e., putamen) and the right IFG. This analysis showed a positive correlation between striatum in TD control subjects but not the WS subjects. These correlations posit that connections between the striatum and right IFG are disrupted in WS and support previous sugges-

tions of frontal impairment in this population (Atkinson *et al.* 2003; Frigerio *et al.* 2006).

Another important structure in the inhibition network is the ACC. Both within- and between-group analyses indicated that TD control subjects had more extensive ACC activity than participants with WS. This region is commonly activated in studies utilizing a Go/NoGo paradigm, a finding thought to reflect neural activity related to longer relative to shorter inhibition time, attention modulation and cognitive control associated with response inhibition (Botvinick *et al.* 2004; Garavan *et al.* 1999; Li *et al.* 2006). Analysis of this structure in WS using structural imaging techniques have demonstrated dACC hypertrophy in WS individuals (Reiss *et al.* 2004), and fMRI studies have shown this region to be overengaged during face and gaze processing (Mobbs *et al.* 2004). Intriguingly, the dACC also has strong connections to the striatum and damage to this circuit often leads to executive dysfunction and poor impulse control in social situations (Masterman *et al.* 1997). Despite the anomalies previously observed in the ACC, the current study suggests that attentional processes in WS may function at a level sufficient to perform our simple Go/NoGo task.

The finding of reduced dlPFC activation in WS, compared with control subjects, is of interest given the role of this prefrontal region in behavioral selection, maintenance of attentional demands, and response target probability (MacDonald *et al.* 2000). The dlPFC is an important component of the cortical behavioral inhibition circuit and is an integral part of the striatal-thalamo-cortical loop (Masterman *et al.* 1997). For example, output from the striatum is crucial in planning and spatial working memory (Owen *et al.* 1998). Other connections to the dACC and SMA may play a role in attention shifting and initiation and suppression of movements, respectively (Garavan *et al.* 1999). Given the basic nature of the present Go/NoGo task, an important goal of future research will be to test this circuit under more demanding and complex conditions (e.g., stop-signal tasks).

An interesting finding was the increased activity in the PCC and precuneus in the WS group compared with the TD group. Elicited modulation of the PCC is anatomically plausible given that the PCC is interconnected with the ACC and receives direct projections from the striatum (i.e., caudate; Cavanna and Trimble 2006; Parvizi *et al.* 2006). One suggestion is that the increased activation of PCC in the WS group reflects the use of a posterior system that might compensate for the decreased engagement of frontostriatal systems. This does not seem intuitive, however, given that a recent study conducted by our group showed abnormal cortical thickness profiles in the PCC (Thompson *et al.* 2005). Moreover, PCC activity in children with ADHD relates to reduced ability to relocate attention following errors (Sergeant 2000) and inhibition failure (Li *et al.* 2006; Rubia *et al.* 2005). Intriguingly, PCC BOLD activity in our TD group was correlated with increased RT. Together, this pattern of results support the notion that PCC activation is related to delayed performance during response inhibition.

Although the results of our study are novel and point to putative neural mechanisms underlying an important facet of the WS cognitive phenotype, several methodological limitations are evident. The most prominent limitation is the difference in IQ between the WS and TD participants. We evaluated the potential for this problem to confound the results by assessing whether IQ was correlated with brain activation and performance in the WS group. The addition of an IQ-matched group would help to support our premise that the neural activation patterns observed in WS are unique to this disorder. Methodologic factors related to

image processing could also potentially influence the observed group differences in BOLD signal. For example, individuals with WS have unusually shaped brains (Schmitt *et al.* 2001) that may be subject to greater warping during normalization to standardized coordinate space than control brains (Eckert *et al.*, in press). This could lead to greater variability in the position of brain regions in subjects with WS compared with control subjects. Despite these limitations, we present plausible neurobiological interpretations for the results of this study and provide valuable data for comparison to results from other imaging and cognitive investigations of WS.

In conclusion, our results provide new evidence that failure to engage frontostriatal systems contributes to deficits in response inhibition in WS. Our results also complement recent findings suggesting that aberrant connectivity between the OFC and amygdala occurs in WS and may underlie deficits in social cognition in affected individuals (Meyer-Lindenberg *et al.* 2005). Indeed, individuals with WS may demonstrate abnormalities in inhibition of inappropriate social behavior on the basis of dysfunction in two critical neural systems: the OFC/amygdala (Meyer-Lindenberg *et al.* 2005) and frontostriatal systems (Atkinson *et al.* 2003; Frigerio *et al.* 2006). Further research into frontostriatal systems in WS holds promise for improving our understanding of a broad range of cognitive and behavioral abnormalities observed in affected individuals in addition to behavioral inhibition such as motor planning deficits and saccadic dysmetria (Atkinson *et al.* 2003).

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