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The neural substrates of cognitive control deficits in autism spectrum disorders

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ABSTRACT

Executive function deficits are among the most frequently reported symptoms of autism spectrum disorders (ASDs), however, there have been few functional magnetic resonance imaging (fMRI) studies that investigate the neural substrates of executive function deficits in ASDs, and only one in adolescents. The current study examined cognitive control – the ability to maintain task context online to support adaptive functioning in the face of response competition – in 22 adolescents aged 12–18 with autism spectrum disorders and 23 age, gender, and IQ matched typically developing subjects. During the cue phase of the task, where subjects must maintain information online to overcome a prepotent response tendency, typically developing subjects recruited significantly more anterior frontal (BA 10), parietal (BA 7 and BA 40), and occipital regions (BA 18) for high control trials (25% of trials) versus low control trials (75% of trials). Both groups showed similar activation for low control cues, however the ASD group exhibited significantly less activation for high control cues. Functional connectivity analysis using time series correlation, factor analysis, and beta series correlation methods provided convergent evidence that the ASD group exhibited lower levels of functional connectivity and less network integration between frontal, parietal, and occipital regions. In the typically developing group, fronto-parietal connectivity was related to lower error rates on high control trials. In the autism group, reduced fronto-parietal connectivity was related to attention deficit hyperactivity disorder symptoms.

1. Introduction

Autism spectrum disorders (ASDs), including autism, high functioning autism, Asperger's Disorder, and PDDNOS, are neurodevelopmental disorders with a prevalence of 1 in 150 (CDC MMWR, 2007). Impairments in executive functions are among the most consistently reported deficits in individuals with ASDs (see Ozonoff, Pennington, & Solomon, 2006; Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006). Executive function deficits in autism generally are assumed to be the result of abnormal prefrontal cortex (PFC) function. However, there have been few published functional magnetic resonance imaging (fMRI) studies of executive functions in individuals with ASDs, and only one has been conducted in adolescents (see Silk, Rinehart, Bradshaw, Tonge, Egan, O'Boyle, et al., 2006). Thus, little is known about the specific brain regions and neural circuits associated with executive deficits in adolescents with ASDs.

1.1. Neural substrates of cognitive control

Cognitive control is a parsimonious and mechanistic term evolving in the field of cognitive neuroscience to refer to what previously have been thought of as executive functions. Cognitive control refers to the ability to flexibly allocate mental resources to guide thoughts and actions in light of internal goals. It involves processing of task-relevant over competing information. Cognitive control must be engaged to represent task-relevant information, to overcome habitual responses, to ignore irrelevant stimuli, to transform mental representations, and to act in novel or rapidly changing conditions (Braver, Cohen, & Barch, 2002; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002). Impairments in cognitive control cause perseveration on over-learned behaviors. When assessed using behavioral measures requiring maintenance of task-relevant information and inhibition of a prepotent response tendency, cognitive control appears to be impaired in adolescents with ASDs (Solomon et al., 2008).

Cognitive control-based approaches are premised on clearly articulated links to neural systems. For example, the neural basis of cognitive control has been specified in the Miller and Cohen (2001) "guided activation hypothesis," which suggests that (1) the

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PFC is specialized for the representation and maintenance of task-relevant information or "context," (2) that context information is maintained in the PFC as a pattern of neural activity; and (3) that context representations mediate cognitive control through interactions that provide top-down biasing that modulates the flow of information in other brain systems that more directly support task performance (Braver et al., 2002; Fuster, 2002; Thompson-Schill, Bedny, & Goldberg, 2005).

Cognitive control has been associated with a reliable network of brain regions including the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC), and the parietal cortex (Curtis, Rao, & D'Esposito, 2004; Yarkoni et al., 2005). DLPFC is recruited when information must be maintained over a delay (Curtis & D'Esposito, 2003), when it is necessary to overcome prepotent response tendencies (D'Esposito & Postle, 2002); and when it is necessary to maintain appropriate context for action (MacDonald, Cohen, Stenger, & Carter, 2000). Better performers on cognitive control tasks activate the PFC more reliably and robustly than poorer performers (MacDonald et al., 2000; Rypma, Berger, & D'Esposito, 2002). Hypoactivation of the PFC during cognitive control tasks is also found in individuals with disorders including schizophrenia (Perlstein, Dixit, Carter, Noll, & Cohen, 2003; Snitz et al., 2005).

The ACC is thought to function as part of a "control loop." In this loop, dorsal ACC signals the occurrence of conflicts in information processing and thereby triggers compensatory adjustments in cognitive control, which serve to reduce conflict in subsequent task performance (Botvinick, Cohen, & Carter, 2004; Carter et al., 1998; Egner & Hirsch, 2005). Magnitude of error-related activity in the ACC has been shown to predict changes in response times and the magnitude of activity in DLPFC on trials immediately following error commission (Kerns, 2006).

The parietal cortex is activated when it is necessary to switch attentional focus (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000) or task sets (Braver, Reynolds, & Donaldson, 2003; Dreher, Koechlin, Ali, & Grafman, 2002; Ravizza & Carter, 2008; Yeung, Nystrom, Aronson, & Cohen, 2006). Some also have argued that the parietal cortex acts as a repository of learned stimulus–response associations that are accessed through top-down biasing by the PFC (Bunge, Kahn, Wallis, Miller, & Wagner, 2003; Wendelken, Bunge, & Carter, 2008).

1.2. Neuroimaging studies of executive functions in autism

The majority of fMRI studies of executive functions including response inhibition, working memory, mental rotation, spatial attention shifting, and response monitoring in individuals with ASDs have shown an overall reduction in brain activation in regions associated with these functions (see Schmitz et al., 2006; Takarae, Minshew, Luna, & Sweeney, 2007 for exceptions). There have been several fMRI studies of response inhibition in ASDs. Kana, Keller, Minshew, and Just (2007) used two versions of a go-no-go task in 12 adults with autism and 12 matched control subjects and found that participants with autism showed less brain activation in areas generally associated with inhibition including the ACC. In a more demanding version of the task that included a working memory load, individuals with autism displayed greater activation in premotor areas. In a cognitive control task involving overcoming a prepotent response tendency and set shifting, Shafritz, Dichter, Baranek, and Belger (2008) found that, participants exhibited control, but not set shifting impairments, and that individuals with ASDs exhibited less neural activity in the PFC, ACC, and parietal cortex relative to control subjects. In a working memory study using a single letter n-back paradigm, Koshino et al. (2005) found that individuals with autism activated posterior regions (inferior temporal and occipital cortices) more than typically developing subjects, and showed a different pattern of temporal connectivity between prefrontal and parietal regions. fMRI studies of spatial attention in adults with ASDs have found that these individuals exhibit less task-related activation in the DLPFC and parietal cortex than control participants during an occulomotor spatial working memory task (Luna et al., 2002), a bilateral visual spatial attention task (Belmonte & Yurgelun-Todd, 2003), and an attention orienting task (Haist, Adamo, Westerfield, Courchesne, & Townsend, 2005). Silk et al. (2006), also showed that adolescents with high functioning autism showed less activation than matched typically developing control subjects in lateral and medial premotor cortex, DLPFC, ACC, and caudate nucleus during a mental rotation task. In a study of response monitoring and the ACC using a saccadic paradigm, Thakkar et al. (2008) found that adults with autism made more antisaccade errors and showed reduced discrimination between error and correct responses in rostral ACC primarily due to abnormally increased ACC activation on correct trials.

A common theoretical framework that has been used to interpret neuroimaging findings in autism research is the underconnectivity hypothesis (Just, Cherkassky, Keller, & Minshew, 2004), which posits that the major neurobiologic abnormalities involved in autism involve alterations in white matter development, functional underconnectivity in large scale neural networks, and functional over-connectivity in small scale networks (Just et al., 2004; Minshew & Williams, 2007). There have now been several studies documenting "underconnectivity" in executive functions in autism in fronto-parietal regions during tasks of planning (Just, Cherkassky, Keller, Kana, & Minshew, 2007), response inhibition (Kana et al., 2007), and in the ACC (Thakkar et al., 2008).

1.3. Relationship to behavioral symptoms

An examination of relationships between control deficits and clinically relevant behavioral symptoms can help to validate a cognitive control-based model, and to improve understanding of the pathophysiology of ASDs, and their co-morbidities. For example, impairments in cognitive control in ASDs may be related to the existence in this population of Attention Deficit Hyperactivity Disorder (ADHD) symptoms (Casey, Nigg, & Durston, 2007; Nigg & Casey, 2005). While current diagnostic nosologies do not allow ADHD and autistic disorders to be diagnosed simultaneously, multiple studies have shown high rates of co-morbid attention deficit disorder (ADD) in individuals with ASDs (e.g. Verté et al., 2006). Brieber et al. (2007) observed that children with ADHD and children with autism displayed comparable ADHD symptoms, gray matter reductions in the left medial temporal lobe, and higher gray matter volumes in left inferior parietal cortex. Parietal atypicalities in both groups were interpreted as related to attention deficits. Functional imaging studies of ADHD have found hypoactivation of the anterior cingulate cortex (Durston et al., 2003) and fronto-parietal abnormalities (Booth et al., 2005; Dickstein, Bannon, Castellanos, & Milham, 2006; Durston et al., 2003). Thus, similar patterns of cingulate and fronto-parietal activity may be observed in individuals with ASDs.

1.4. Hypotheses

In the current study, we used event-related fMRI, to investigate the neural correlates of cognitive control in a large sample of adolescents aged 12–18 with ASDs and typical development, and to examine the relationships between indices of neural activity and behavioral measures of inattention. The Preparing to Overcome Prepotency (POP) Task, which assesses the effects of advance preparation on overcoming stimulus–response incompatibility has been examined in typically developing young adults, schizophrenia patients, and older adults. Studies have found increased activation in DLPFC (BA 9), anterior frontal (BA 10), parietal cortex (BA 7 and

BA 40) and ACC (BA 32) regions during the cue phase of the task. In the probe phase, where subjects execute a motor response, medial frontal (BA 6 and BA 32), and left parietal lobule (BA 7 and BA 40) activation has been observed (Barber & Carter, 2005; Rosano et al., 2005; Snitz et al., 2005). Based on these results as well as those from fMRI studies in autism showing a general pattern of hypoactivation in frontal and parietal regions, our first hypothesis was that individuals with ASDs would show significantly less neural activation in prefrontal, parietal, and anterior cingulate cortices relative to control subjects during the cue phase of the task. Second, given the suggestion that autism is a disorder of reduced connectivity and that impairments in cognitive control could be due to reduced connectivity between frontal, parietal, and ACC regions (Kana et al., 2007), we hypothesized the autism group would show reduced connectivity and integration between these brain regions. Finally, based on the ADHD literature, we hypothesized that activation in fronto-parietal and ACC regions would be related to task performance and ADHD symptoms.

This study helps fill the gap in the pediatric neuroimaging literature on executive functions in ASDs. It employs a large stimulant and antipsychotic-free sample with a gender ratio consistent with the patient population; uses two forms of functional connectivity analysis – including the time series correlation method that has been used in autism research, and the beta series method, which is a natural extension of this method – to establish convergent validity of findings; and examines brain–behavior relationships by investigating relationships between activation and connectivity patterns using measures of attention deficit disorder symptoms.

2. Methods

2.1. Participants

Thirty-two subjects with ASDs and 32 subjects with typical development were enrolled in the study. However, 10 subjects with ASDs and 9 subjects with typical development were excluded due to excess motion in the scanner. This left 22 subjects with ASDs (mean age = 15.2 years, standard deviation [SD] = 1.7) and 23 subjects with typical development (mean age = 16.0, SD = 2.0) who are described in this manuscript. Based on the male to female gender ratio of approximately 4:1 in the population of individuals with autism (Nyden, Hjelmquist, & Gillberg, 2000), the study included 5 female subjects in each group. Two participants were African Americans, 2 were Asian or Pacific Islanders, and 1 was Hispanic. They were recruited through community providers (e.g., psychiatrists, psychologists, neurologists, pediatricians, speech and language pathologists, and advocacy groups), and the M.I.N.D. Institute's Subject Tracking System database. All subjects were right-handed and had a Full Scale IQ of at least 70 on the Wechsler Abbreviated Scales of Intelligence (WASI; Wechsler, 1999). Of the 22 participants with an ASD, 10 were diagnosed with Autistic Disorder (high functioning autism), and 12 were diagnosed with Asperger's Disorder, according to criteria set by the DSM-IV-TR (American Psychiatric Association, 2000), ADOS-G (Lord et al., 2000), and Social Communication Questionnaire using an ASD cutoff score of 15 and above (SCQ; Berument, Rutter, Lord, Pickles, & Bailey, 1999). The decision to include individuals with both high functioning autism and Asperger's Disorder derives from studies showing that, despite DSM diagnostic categories, it is difficult to reliably distinguish between the two disorders (e.g. Howlin, 2003; Macintosh & Dissanayake, 2004; Ozonoff & Griffith, 2000), and that there is no empirical distinction in symptomatology and outcome by the time children reach the age of participants in this protocol (Howlin, 2003; Szatmari, Bryson, Boyle, Streiner, & Duku, 2003). Exclusion criteria for ASD subjects included diagnoses of autism with known genetic etiologies (i.e. fragile X syndrome, tuberose sclerosis), and known psychopathology reported by parents at the time of initial enrollment. Despite this exclusion, 55% of participants with ASDs and none of those with typical development met criteria for clinically significant ADHD symptoms as assessed by the Conners' Parent Rating Scale (Conners, Sitarenios, Parker, & Epstein, 1998). Best efforts were used to recruit a sample not taking psychotropic medications. However, three children in the ASD group were taking psychostimulants and were asked to discontinue these medications for a period of 24 h prior to scanning. Five children in the ASD group were taking selective serotonin reuptake inhibitors (SSRIs). Typically developing individuals reported no neurodevelopmental or learning disorders and had a score of less than 11.0 on the Social Communication Questionnaire. See Table 1 for a summary of participant characteristics.

All subjects gave written assent along with consent from their legal guardians to participate in this study, which was approved by the University of California, Davis' Institutional Review Board.

2.2. Qualification measures

2.2.1. Wechsler Abbreviated Scales of Intelligence (WASI; Wechsler, 1999)

The WASI was developed to provide a short and reliable means of assessing intelligence in individuals aged 6–89. The WASI produces the three traditional Verbal, Performance, and Full Scale IQ scores. It consists of four subtests: Vocabulary, Block Design, Similarities, and Matrix Reasoning. These scales were chosen due to their strong association with overall intellectual functioning. These scales provide standard scores with a mean of 100 and a Standard Deviation of 15. The WASI is nationally standardized, and exhibits strong psychometric properties. It has exhibited acceptable levels of internal consistency, test–retest reliability, and validity.

2.2.2. Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003)

Parents were asked to complete the SCQ, a brief 40-item parent-report screening questionnaire to evaluate communication and social skills. It may be used for individuals 4 years of age and older. It contains parallel questions to those included on the ADI-R (Lord, Rutter, & Le Couteur, 1994), which is the "gold standard" parent-report diagnostic measures in the field presented in a briefer yes/no format. The Lifetime Form, which focuses on the child's entire developmental history including early symptoms, was used in this study. Based on a total sample of 200 (160 with pervasive developmental disorder or PDD and 40 typically developing children), Berument et al. (1999) reported that the mean SCQ score for non-intellectually impaired individuals was 11.2, while that of individuals with PDD was 22.3 and that of individuals with autism was 24. A cutoff point of 15 or over gave a sensitivity of .96 and a specificity of .80 for autism versus other diagnoses. Thus a cutoff score of 15 was recommended. There was high correlation with the ADI algorithm score. Based on this work, a cutoff score of 11 or below was used to screen for exclusion. To construct scores for the autism domains, we aggregated items loading onto ADI domains of reciprocal social interaction, language, and restricted and repetitive patterns of behavior and interests. If items were indicative of the construct assessed by the domain, we assigned a score of "1" to the item. These were tallied to form a composite score for the domain. Internal consistency reliability (Cronbach's alpha) across these social, communication, and repetitive behavior scales were .95, .88, and .92, respectively.

2.2.3. Autism Diagnostic Observation Schedule-Generic (ADOS-G; Lord et al., 2000)

Once qualification based on the WASI was established, participants with ASDs were administered module 3 or 4 of the ADOS-G, a semi-structured interactive session and interview protocol that offers a standardized observation of current

Table 1
Participant characteristics.

	ASD group (n = 22)		Typically developing group (n = 23)	
	M (SD)	Range	M (SD)	Range
Age (months)	182 (20)	150–218	191 (25)	150–225
VIQ	107 (16)	80–145	114 (13)	86–136
PIQ	105 (14)	77–135	111 (12)	83–130
FSIQ	107 (14)	85–132	113 (11)	83–131
SCQ total	21.5 (6)	15–37	3 (2)	0–8
SCQ social behavior domain	9 (4)	3–16	1 (1)	0–4
SCQ repetitive behavior domain	5 (2)	3–9	0 (1)	0–2
SCQ communication domain	7 (2)	2–12	1 (1)	0–4
ADOS comm + social interaction	10 (3)	7–18	–	–
ADOS communication domain	3 (2)	1–8	–	–
ADOS social interaction domain	7 (2)	4–13	–	–
ADOS restricted interests domain	1 (1)	0–3	–	–

social-communication behavior. Each module has approximately 10 standardized interactional "presses." Participants are rated based on their responses to these social presses, and scored for communication, reciprocal social behavior, and repetitive behaviors and stereotyped interest patterns. An algorithm score, that combines the communication and reciprocal social interaction domains, is the basis for diagnostic classification. Lord et al. (2000) showed that for modules 3 and 4, mean inter-rater agreement was 88% across all items. Inter-rater reliability on all item domains ranged from .82 (restricted and repetitive behaviors) to .93 (social behaviors). Test–retest reliability ranged from .59 (repetitive behaviors) to .78 (social behaviors). Internal consistency reliability was assessed using Cronbach's alphas, which ranged from .91 to .94 for total social and communication items. Inter-rater agreement in diagnostic classification based on the ADOS-G algorithm for all modules exceeded 90%.

2.3. Behavioral measures

2.3.1. Conners' Parent Rating Scale-Revised (Long) (Conners et al., 1998)

The parents of both groups were asked to complete this questionnaire, which helps assess attention deficit/hyperactivity disorder and other problem behaviors. Subscales for cognitive problems/inattention, and hyperactivity, as well as an overall Conners' ADHD index, and DSM-related indices – DSM-IV: inattention, DSM-IV: hyperactivity/impulsiveness, and DSM-IV: total – are produced by this rating instrument. In this study, the DSM-IV total symptoms measure was used. Standard *T* scores above 55 are considered clinically significant. This 80-item version takes 15–20 min to complete and has been proven reliable and valid with over 8000 participants (Conners et al., 1998).

2.4. fMRI measures

Preparing to Overcome Prepotency "POP" task (Barber & Carter, 2005; Rosano et al., 2005; Snitz et al., 2005; Solomon, Ozonoff, Cummings, & Carter, 2008). The POP task is designed to study cognitive control involved in context processing (maintaining a cue over a delay and then overcoming a prepotent response tendency). A colored cue, which is presented for 500 ms, instructs subjects to perform one of the two task conditions. A green cue signals the subject to press the key on the same side that the target (an arrow) points to. The target is presented 7500 ms after the cue and is on the screen for 500 ms. See Fig. 1. The cue of the next trial is presented 11,500 ms after the target stimulus. A red cue signals the subject to press the key on the opposite side that the arrow points to. Green trials involve a response that is compatible with the stimuli (an arrow pointing right means respond with a right button press), occur more often (75% of the time), and are primed at the beginning of each block by three repeated presentations of the green stimulus, which are not analyzed. Thus, green trials are "prepotent" trials. Red trials involve an incompatible response (an arrow pointing left means respond with a right button press), occur less often (25% of trials), and necessitate inhibition of a prepotent response tendency since green trials are more frequent and are primed. Mean reaction times (trimmed for outliers more than two standard deviations from the mean), and error rates were recorded for each trial type.

The task was administered using a slow event-related design. Each subject performed a brief practice block in the scanner (no data were collected for the practice trials) followed by 4 runs of 24 trials (20 s/trial). Thus, each run lasted 480 s with brief breaks lasting a maximum of 3 min in between. There were a total of 24 red trials and 72 green trials. Subjects missing more than 60% of a trial type were excluded from the analysis. This resulted in losing one subject who also showed excess motion. Within each run, trials of the POP task were presented in a pseudorandom order. Activation during green minus baseline, red minus baseline, and red minus green trials during the cue (considered the strongest measure of cognitive control), were examined.

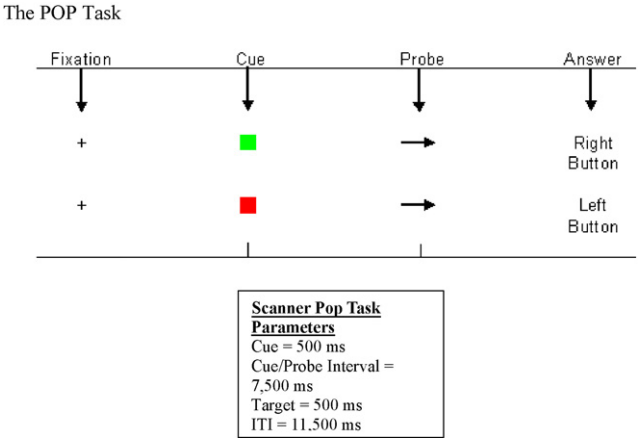

Fig. 1. The POP task.

2.5. fMRI data acquisition

Structural and gradient-echo echo-planar images were acquired on a 3.0-T Siemens Trio magnetic resonance imaging scanner with an eight-channel phased array head coil. Cushions, tape, and pre-training in a mock scanner were used to minimize head motion. Earplugs and headphones were used to dampen scanner noise and to enable communication with the participants. Both structural and functional images were acquired at each scan.

Thirty-six interleaved (odds then evens) whole-brain axial slices (thickness = 4.0 mm) were acquired in a plane parallel to the anterior commisure–posterior commisure (AC–PC) line. Each 20-s trial was sampled by ten 2.0 s functional volumes using a single-shot T2*-weighted echo-planar sequence (TR = 2000 ms, TE = 24 ms, flip angle = 90°, FOV = 22 cm, 64 × 64 voxels). A standard T1-weighted pulse sequence was used to obtain structural images in the same plane as the functional images.

The task was presented on a desktop computer interfaced with a response box and a color LCD projector using the E-prime software package. Stimuli were rear-projected onto a screen viewed through a mirror attached to the head coil. Behavioral data were analyzed using error rates and trimmed mean corrected RTs as dependent measures. The first three acquisitions of each run were discarded to allow for fMRI signal to reach steady-state.

2.6. Data preprocessing and analysis

Imaging data were analyzed using SPM2 software (Wellcome Department of Cognitive Neurology, London, United Kingdom). Connectivity analyses were implemented using Matlab (MathWorks, Natick, MA) scripts designed for this study. Images were corrected for slice acquisition timing using SPM2's Fourier phase shift interpolation to the first slice. They were then realigned to correct for motion using the mean functional volume as a reference, a least squares approach, and a six-parameter (rigid body) spatial transform. Next, images were spatially normalized to the Montreal Neurological Institute (MNI) template using a 12-parameter affine, 3 × 2 × 3 DCT basis and resampled to 2-mm cubic voxels, then smoothed with a three-dimensional Gaussian kernel (8 mm FWHM). They were then visually checked for quality control. Data from participants moving more than 3 mm in any direction or rotating their heads more than 4 degrees across the session were excluded from the experiment. This resulted in us excluding approximately 30% of subjects from the analysis. Excluded subjects came from both the ASD and the typically developing groups in equal proportions. A small number of trials (total of 25 in all subjects) for which there were motion spikes were modeled as "error" trials and thereby removed from the analysis. Also, one subject with ASD and one subject with typical development exhibited significant motion between the third and fourth runs and these two runs were not used for analyses.

Statistical analysis was performed on individual and group data using the general linear model (GLM) with multiple regressions as implemented in SPM2. Estimations were made using the ordinary least squares (OLS) method, SPM2's canonical HRF, a high-pass filter of 100 s, and SPM2's AR(1) model. Temporal and dispersion derivatives, as well as motion estimates were used as covariates of non-interest in the model. The cue and probe phases of the task were modeled separately and four contrasts were created at the first level (intrasubject) analysis: CueRed–CueGreen, CueGreen–CueRed, CueRed–baseline and CueGreen–baseline. Analyses included correct trials only (Carter & Pine, 2006). Group (second level) analyses were performed by using the intrasubject contrast images in random-effects group contrasts (one sample and two sample *t*-tests for within group and between group comparisons, respectively). Because our primary interest was in investigating between group differences in cognitive control related brain activation, for the cue phase of the task, we first constructed a mask of regions which represented a conjunction of regions across both groups showing activation of a *t* threshold of 2.5 (approximately $p = .01$ uncorrected for a cluster of 10 contiguous voxels). This mask consisted of frontal, ACC, parietal, and occipital regions previously shown to be activated during the POP task (e.g. Barber & Carter, 2005; Rosano et al., 2005; Snitz et al., 2005). Within this search space, we report group differences significant at $p < .05$ corrected for multiple comparisons using the false discovery rate method (FDR; Genovese, Lazar, & Nichols, 2002).

2.7. Functional connectivity analysis

Two methods were used to analyze functional connectivity between prefrontal and other regions. First, the times series correlation method (Koshino et al., 2005), which has been used extensively in the autism literature, was adapted. In this method, frontal regions and other regions identified through a within group analysis were correlated with each other. In this first connectivity analysis, ROIs corresponding to those found in Table 3 were used. A sphere of 10 mm radius for each corresponding ROI was defined with Pickatlas (Lancaster et al., 2000). Time series were extracted from these ROIs using the MarsBaR Tool Box (Brett, Anton, Valabregue, & Poline, 2002). For each participant, for correct trials only, the mean across all trials of a given type for the time course in signal intensity change baselined to the first scan was computed for each ROI. Correlations between time series of pairs of ROIs were then calculated for red trials and green trials separately because it would be difficult to interpret differences in connectivity inherent in a red minus green subtraction. Correlation coefficients were transformed using a Fisher *r*-to-

Table 2
POP task variables summary.

	ASD group ($n = 20$)[a]		Typically developing group ($n = 23$)		F-statistic	p-Value
	M (SD)	Range	M (SD)	Range		
Green trials						
Mean ER	0.02 (0.02)	0.00–0.06	0.01 (0.01)	0.00–0.04	1.304	.200
Mean RT for correct trials	689 (245)	403–1162	663 (224)	290–1196	0.364	.718
Red trials						
Mean ER	0.26 (0.20)	0.00–0.58	0.11 (0.09)	0.00–0.33	3.507	.002
Mean RT for correct trials	718 (285)	425–1252	716 (238)	318–1271	0.053	.958

[a] Two ASD subjects were removed from the analysis because response times were more than two standard deviations away from the mean.

z' transformation. Mean z'-transformed values were computed across participants and ROI pairs, and then converted back to correlation coefficients. Consistent with hypotheses of prefrontal deficits in ASDs and with previous studies of regions activated by the POP task, the within group analysis produced prefrontal seeds in BA 9 right and BA 10 bilaterally. Student's t-tests were used to examine connectivity differences between prefrontal regions and posterior regions identified in the conjunction of the within group maps for both red and green trials.

Next, a factor analysis of the functional connectivities for correct red − baseline trials was performed to examine the grouping of the ROIs into networks based on the similarity of their time courses (Kana et al., 2007; Koshino et al., 2005). The logic underlying this approach is that each factor represents a neural network used for task performance. Factor loadings represent the degree to which each of the ROIs correlates with each of the factors. For each ROI pair, mean z'-transformed values of the functional connectivity measures were computed across participants. Mean z'-transformed values were then converted back to correlation coefficients, and a correlation matrix was constructed for each group. An exploratory factor analysis (see Peterson et al., 1999) was then performed for each group separately for red and green trials. Factors with eigen values > 1.0 were retained. Factor loadings of >.5 were interpreted.

A second method of analyzing functional connectivity, the beta series correlation method (Rissman, Gazzaley, & D'Esposito, 2004), was used as a natural extension to the time series correlation method to include trial phase specific beta series correlations across trials and to establish convergent validity with a mean time series approach. In this method, we again used the prefrontal seed regions identified by a conjunction of the within group analyses, however, there were no restrictions put on the regions that could be identified as showing connectivity differences with the seeds. This method also differed from the time series method in that it correlated trial specific betas across groups, as opposed to correlating mean time series across groups. In the beta series method, a GLM including every stage of every trial was modeled with a separate covariate to obtain trial-to-trial parameter estimates of stage-specific activity. Parameter values (betas) from each trial were sorted according to task stage into sets of condition specific betas or "beta series," and correlated across brain regions. Stage-specific whole-brain correlation maps were obtained by calculating the correlations of the PFC (BA 9 and BA 10) seed region's beta series with that of all brain voxels. Fisher r-to-z transformations were applied to the correlation coefficients of all brain voxels to normalize their distribution. Condition specific seed correlation maps were generated. z-Transformed maps were normalized into MNI space. To control for Type I error, group level random-effects t-tests were conducted to identify voxels for which the mean of the individual subject's transformed correlation coefficients were reliably greater than 0.

3. Results

3.1. Behavioral performance

To examine differences in trimmed mean reaction times for red versus green cues, a 2×2 analysis of variance (ANOVA) was performed where trial type (red versus green) was the within subjects factor, and group (ASD versus typical) was the between subjects factor. For mean reaction times on red versus green trials, there was a main effect of trial type ($F(1, 43) = 24.4$, $p < .001$, $\eta_p^2 = .362$), however the main effect of group and the interaction of trial type and group were not significant. Analysis of simple effects revealed that both groups were significantly slower on red versus green trials.

A similar 2×2 ANOVA analysis of error rates revealed a main effect of trial type ($F(1, 43) = 63.06$, $p < .001$, $\eta_p^2 = .60$), a main effect of group ($F(1, 43) = 12.83$, $p < .001$, $\eta_p^2 = .67$), and a group by trial type interaction ($F(1, 43) = 11.46$, $p < .005$, $\eta_p^2 = .21$). A post hoc comparison showed that the error rate for red trials in the ASD group was significantly higher than that for the control group (26.8% versus 11.4%; $t(43) = 3.49$, $p < .005$), and there was no difference for green trials. See Table 2.

These findings are similar to those previously reported (Solomon et al., 2008), and replicate the cognitive control difficulties of individuals with ASD on this task.

3.2. Imaging results: univariate analysis

The primary contrast used to study cognitive control in univariate analyses is the between group contrast of activation on red minus activation on green trials during the cue phase of the task. A significance threshold with a cluster size of 10 contiguous voxels and imagewise FDR correction of $p < .05$ was used for this analysis (Genovese et al., 2002). As noted above, a mask including frontal, ACC, parietal, and occipital regions previously shown to be activated during the POP task was used. See Table 3 for the within group activations included in this mask.

There were significant between group differences for the control minus autism group in prefrontal regions including anterior PFC (BA 10) bilaterally and left premotor (BA 6) areas, as well as superior parietal lobule/precuneus (BA 7) bilaterally and left inferior parietal cortex (BA 40). Visual areas including right BA 17 and left BA 18 also showed significantly greater activation. Despite findings of compensatory processing in areas outside those used in cognitive control by other researchers (e.g. Kana et al., 2007 and the premotor cortex; and Koshino et al., 2005 and the inferior temporal and occipital areas), in a whole-brain voxel-by-voxel group comparison there were no areas for which the ASD group showed greater activation in the cue than the typically developing subjects. See Table 4. Analyses also were repeated without the five subjects with ASDs who were taking SSRIs. Imagewise FDR corrected results increased to be significant at a trend level ($p < .08$), likely due to the loss of power.

In order to further understand the reduced activation in the red minus green contrast in the ASD group compared to controls, we decomposed this subtraction and examined separate contrasts of red minus baseline and green minus baseline. Consistent with the behavioral data, the groups did not differ significantly on activation to green minus baseline trials on either phase of the task, however there was a significant difference in activation on red minus baseline trials in the cue phase of the task. See Fig. 2 which shows renderings for both groups.

In the between group analysis of red trials during the cue phase of the task, using the same masking strategy as above, multiple prefrontal (BA 9 and BA 10 left), parietal (BA 7 bilaterally) and occipital visual areas (BA 19 bilaterally) were more active in typically developing individuals (Table 5).

3.3. Imaging results: connectivity analysis

First we examined connectivity using the time series correlation method and factor analysis. Connectivity between prefrontal seed regions in the PFC (BA 9, left) and anterior PFC (BA 10, bilaterally) and the cingulate, parietal cortex and occipital cortex regions

Table 3
Regions of activation for red trials minus green trials during the cue phase in controls ($n = 23$) and patients ($n = 22$) for $T > 2.5$. Statistical values were produced from SPM using $p = .01$ and $k = 10$. Only correct trials used.

Region[a]	Cluster size	Voxel p-value		Approximate Talairach coordinates[b]		
		FDR-corrected	Uncorrected	x	y	z
Controls						
LH lingual gyrus (BA 17)	1,810	0.033	0.000	−20	−89	3
LH inferior parietal lobule (BA 40)	11,623	0.033	0.000	−55	−43	37
RH middle occipital gyrus (BA 18)	689	0.033	0.000	26	−85	8
RH middle temporal gyrus	1,465	0.033	0.000	55	−35	−2
LH middle frontal gyrus (BA 11)	203	0.041	0.001	−30	48	−11
RH cingulate gyrus (BA 32)	106	0.049	0.001	12	21	36
RH superior frontal gyrus (BA 6)	871	0.055	0.001	2	5	53
LH superior temporal gyrus (BA 38)	137	0.057	0.001	−48	13	−11
RH superior frontal gyrus (BA 10)	155	0.061	0.002	28	54	−1
RH middle frontal gyrus (BA 6)	128	0.065	0.002	34	−1	65
LH precentral gyrus (BA 6)	255	0.068	0.002	−44	2	35
Cingulate gyrus (BA 23)	129	0.076	0.003	0	−16	25
LH superior frontal gyrus (BA 10)	153	0.080	0.004	−22	44	27
LH middle frontal gyrus (BA 9)	146	0.081	0.004	−36	31	30
RH superior frontal gyrus (BA 6)	16	0.094	0.006	22	9	66
RH inferior frontal gyrus (BA 47)	13	0.097	0.007	32	25	−1
Patients						
RH middle temporal gyrus (BA 21)	20	0.997	0.003	51	3	−17
LH superior temporal gyrus (BA 22)	34	0.997	0.003	−51	10	−4
LH middle temporal gyrus (BA 21)	37	0.997	0.004	−50	3	−20
RH cingulate gyrus (BA 23)	79	0.997	0.004	4	−28	27

[a] Regions were defined by using Talairach Daemon and the "Nearest gray Matter" option (Lancaster et al., 1997; Lancaster et al., 2000; Maldjian et al., 2003).
[b] Approximate Talairach coordinates were derived by using a Matlab function written by Matthew Brett (http://www.imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal.m) to convert the MNI coordinates given by SPM.

identified in the conjunction map were examined for the groups. See Table 6. During red cues, functional connectivity between right BA 10 and visual areas including BA 17 left and BA 18 left was significantly less in individuals with ASDs ($t(43) = 2.49$, $p = .018$ and $t(43) = 2.10$, $p = .042$, respectively). For green cues, connectivity between left BA 10 and other regions including right premotor (BA 6; $t(43) = 2.89$, $p = .007$), left parietal cortex (BA 7; $t(43) = 3.3$, $p = .002$), left (BA 18; $t(43) = 2.62$, $p = .012$), and posterior (BA 23; $t(43) = 3.83$, $p = .000$) and dorsal anterior cingulate ($t(43) = 2.67$, $p = .011$) exhibited significantly lower connectivity in the ASD group. Connectivity for green cues for BA 9 left and BA 7 left ($t(43) = 2.41$, $p = .020$), posterior cingulate ($t(43) = 2.82$, $p = .007$), and visual cortex (18 left; $t(43) = 2.46$, $p = .019$) also showed significantly less connectivity individuals with ASDs.

To examine neural networks involved in responding to red trials, we conducted a factor analysis to examine the groupings of the ROI pairs into networks based on the similarities of their time courses. In the cue phase of the task, the factor solution for the autism group, which explained 70.4% of the variance, consisted of two factors, whereas the typically developing group only exhibited one factor, accounting for 76% of the variance. As shown in Table 7, in the autism group, the prefrontal (BA 9 and BA 10), cingulate (BA 32 and BA 23) and inferior parietal (BA 40) cortices exhibited similar time courses and loaded onto the same factor, whereas superior parietal lobule (BA 7) and visual areas (BA 17 and BA 18) loaded onto the second factor. This suggests that, in the cue phase, the autism group uses a different and less well-integrated system of neural networks

Table 4
Between group activation for red trials minus green trials during the cue phase of the task ($n = 45$). Voxel-wise of FDR < 0.05 and $k = 10$ was used. A conjunction mask of voxels significant in both groups at $T > 2.5$ ($p = .01$) was applied to images. Only correct trials are reported.

Region[a]	Cluster size	Voxel p-value		Approximate Talairach coordinates[b]		
		FDR-corrected	Uncorrected	x	y	z
Controls versus patients						
RH precuneus (BA 7)	1260	0.043	0.000	24	-45	41
LH radiatio optica	435	0.043	0.000	−32	−65	12
LH postcentral gyrus (BA 40)	195	0.043	0.001	−51	−30	51
LH middle frontal gyrus (BA 10)	86	0.043	0.001	−28	50	−4
RH superior frontal gyrus (BA 10)	46	0.044	0.001	28	51	1
LH middle occipital gyrus (BA 18)	257	0.044	0.002	−24	−87	17
LH precuneus (BA 7)	396	0.046	0.002	−16	−60	45
RH declive	23	0.046	0.002	22	−81	−18
LH superior frontal gyrus (BA 10)	22	0.049	0.003	−20	46	27
RH culmen	14	0.049	0.004	24	−63	−24
LH superior temporal gyrus (BA 22)	33	0.049	0.005	−55	−41	6
LH supramarginal gyrus (BA 40)	52	0.049	0.005	−59	−43	30
LH lingual gyrus (BA 18)	28	0.049	0.005	−22	−80	−9
LH inferior parietal lobule (BA 40)	26	0.049	0.005	−50	−35	37
LH middle frontal gyrus (BA 6)	12	0.049	0.005	−28	−5	57
RH cuneus (BA 17)	20	0.049	0.006	24	−81	11

[a] Regions were defined by using Talairach Daemon and the "Nearest gray Matter" option (Lancaster et al., 1997; Lancaster et al., 2000; Maldjian et al., 2003).
[b] Approximate Talairach coordinates were derived by using a Matlab function written by Matthew Brett (http://www.imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal.m) to convert the MNI coordinates given by SPM.

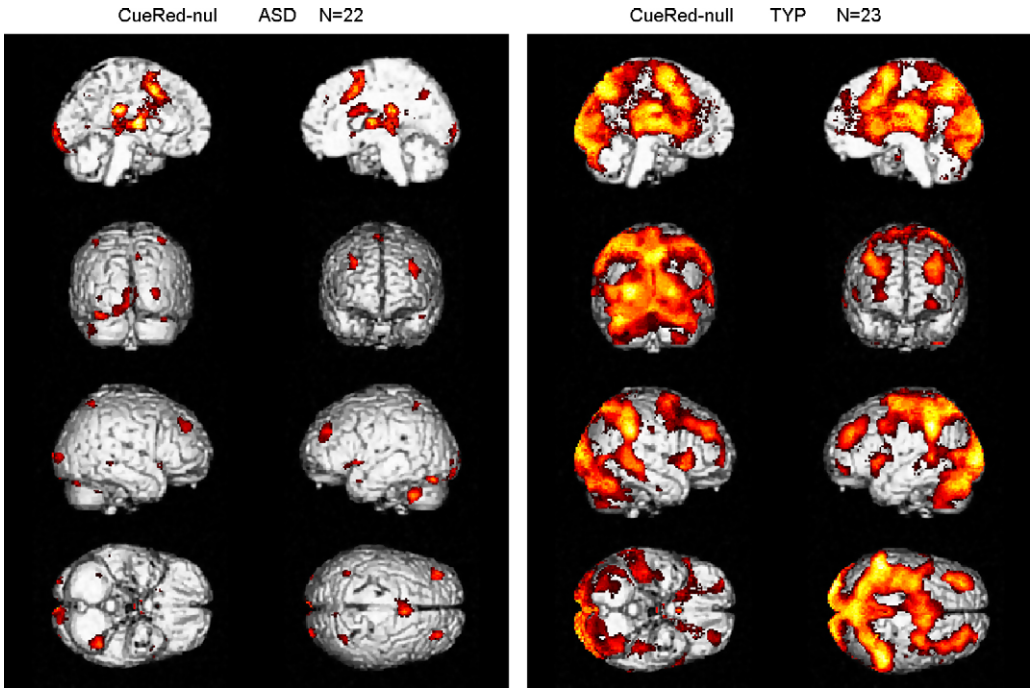

Fig. 2. Renderings of cue period activation on the red trials.

to accomplish the task of maintaining the more difficult red cue online.

As shown in Table 8, the beta series correlation method provided some convergent validity for findings of the time series correlation method, but also extended these findings given that this method did not place a priori restrictions on the regions that could exhibit connectivity with the prefrontal seed.

In this analysis, group connectivity differences were only found for the left anterior PFC (BA 10) seed. During red trials in the cue phase, functional connectivity between this seed region was significantly greater in typically developing participants for areas of the parietal cortex (BA 7 and BA 40), right anterior cingulate (BA 24), and visual cortex (BA 18). Unlike time series correlation, the beta series method also showed reduced connectivity in the ASD group between the anterior PFC seed and striatal (caudate) and medial temporal lobe (hippocampus and amygdala) regions, as well as the fusiform gyrus. See Fig. 3.

Table 5
Regions of activation for red trials minus baseline during the cue phase in the group comparison ($n = 45$). Voxel-wise FDR < 0.05 and $k = 10$ was used. A mask, created by combining significant clusters at $T = 2.5$ in the control group with significant clusters in the patient group, was applied to images. Only correct trials were used.

Region[a]	Cluster size	Voxel *p*-value		Approximate Talairach coordinates[b]		
		FDR-corrected	Uncorrected	*x*	*y*	*z*
Controls versus patients						
RH cingulate gyrus (BA 31)	2387	0.048	0.000	26	−43	37
LH inferior parietal lobule (BA 40)	1088	0.048	0.000	−50	−37	39
LH middle frontal gyrus (BA 6)	190	0.048	0.000	−26	−7	57
LH postcentral gyrus (BA 7)	126	0.048	0.000	−8	−49	67
RH hippocampus	19	0.048	0.000	34	−30	−9
RH parahippocampal gyrus (BA 19)	35	0.048	0.000	40	−48	2
LH inferior frontal gyrus (BA 9)	55	0.048	0.000	−57	9	27
RH superior parietal lobule (BA 7)	89	0.048	0.000	20	−63	57
LH precuneus (BA 7)	393	0.048	0.001	−14	−62	51
LH superior frontal gyrus (BA 10)	136	0.048	0.001	−22	46	27
LH posterior cingulate (BA 30)	22	0.048	0.001	−30	−67	11
LH middle occipital gyrus (BA 37)	70	0.048	0.001	−44	−68	3
RH insula (BA 13)	35	0.048	0.001	36	−36	18
LH superior frontal gyrus (BA 6)	24	0.048	0.001	−16	9	60
RH precuneus (BA 7)	40	0.048	0.001	16	−66	44
RH cuneus (BA 7)	32	0.048	0.001	18	−77	13
LH fusiform gyrus (BA 19)	40	0.048	0.001	−38	−69	−13
RH declive	30	0.048	0.001	40	−67	−17
RH postcentral gyrus (BA 3)	14	0.048	0.001	22	−33	70
LH middle frontal gyrus (BA 9)	13	0.048	0.001	−44	8	36
LH fusiform gyrus (BA 19)	19	0.048	0.001	−26	−82	−11
LH superior frontal gyrus (BA 6)	13	0.048	0.002	−2	1	66
RH paracentral lobule (BA 4)	20	0.048	0.002	4	−38	65

[a] Regions were defined by using Talairach Daemon and the "Nearest gray Matter" option (Lancaster et al., 1997; Lancaster et al., 2000; Maldjian et al., 2003).

[b] Approximate Talairach coordinates were derived by using a Matlab function written by Matthew Brett (http://www.imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal.m) to convert the MNI coordinates given by SPM.

Table 6
z-Transforms for correlation coefficients for pairs of ROIs.

	ASD group ($n=22$)		Typical group ($n=23$)		*F*-statistic	*p*-Value
	Mean	SD	Mean	SD		
BA 10R						
Red trials for cue phase						
BA 6R	0.442	0.69	0.748	0.68	1.505	0.140
BA 7L	0.432	0.71	0.730	0.64	1.481	0.149
BA 17L	0.501	0.93	1.079	0.58	2.489	0.018
BA 18L	0.482	0.65	0.902	0.69	2.097	0.042
BA 23	0.689	0.87	0.933	0.69	1.042	0.303
BA 32R	0.838	0.71	0.727	0.61	−0.557	0.581
BA 40L	0.588	0.64	0.772	0.65	0.955	0.345
Green trials for cue phase						
BA 6R	0.518	0.72	0.956	0.76	1.980	0.054
BA 7L	0.491	0.67	0.792	0.68	1.494	0.142
BA 17L	0.556	0.67	0.891	0.62	1.741	0.089
BA 18L	0.549	0.65	0.803	0.66	1.302	0.200
BA 23	0.757	0.73	0.966	0.71	0.969	0.338
BA 32	0.720	0.70	0.872	0.39	0.910	0.369
BA 40L	0.487	0.75	0.779	0.85	1.224	0.225
BA 10L						
Green trials for cue phase						
BA 6R	0.627	0.85	1.240	0.52	2.891	0.007
BA 7L	0.399	0.72	1.103	0.72	3.284	0.002
BA 17L	0.551	0.49	0.973	0.55	2.721	0.009
BA 18L	0.513	0.65	1.034	0.68	2.619	0.012
BA 23	0.606	0.57	1.405	0.81	3.826	0.000
BA 32	0.768	0.65	1.236	0.52	2.673	0.011
BA 40L	0.768	0.58	0.980	0.64	1.159	0.253
BA 9L						
Green trials for cue phase						
BA 6R	0.744	0.92	1.075	1.04	1.246	0.220
BA 7L	0.472	0.70	1.017	0.82	2.408	0.020
BA 17L	0.507	0.81	0.829	0.69	1.434	0.159
BA 18L	0.197	0.79	0.722	0.62	2.456	0.019
BA 23	0.592	0.69	1.294	0.96	2.823	0.007
BA 32	1.129	0.70	1.364	0.77	1.071	0.290
BA 40L	0.650	0.89	0.853	0.55	0.913	0.368

3.4. Correlations with behavior

First, we examined brain behavior correlations related to task performance for both groups. For the typically developing group, functional connectivity between BA 9 and superior parietal cortex (BA 7, left; $r=-.42$, $p=.047$) was inversely related to red trial error rates. See Fig. 4. No comparable clear relationship between fronto-parietal connectivity and performance emerged for the ASD group.

To examine the relationship between attention problems and cognitive control in individuals with ASDs, we correlated fronto-parietal connectivity on red minus green trials with scores on the aggregate DSM ADHD Index from the Connor's Scales. We found a significant inverse relationship between connectivity between the BA 9 left and BA 40 left for the Connors DSM-IV total ADHD score ($r=-.43$, $p=.047$). See Fig. 5.

Table 7
Results of factor analysis.

Region	ASD group		Control group
	F1	F2	F1
LH BA 7	–	0.631	0.873
LH BA 9	0.914	–	0.769
LH BA 10	0.868	–	0.905
RH BA 10	0.721	–	0.842
LH BA 17	–	0.905	0.885
LH BA 18	–	0.855	0.901
RH BA 18	–	0.884	0.891
BA 23	0.592	–	0.912
RH BA 32	0.925	–	0.852
LH BA 40	0.592	–	0.811

4. Discussion

The first hypothesis of this study was largely confirmed. In the cue phase of the task, a between group comparison for the red minus green contrast indicated that adolescents with ASDs showed less frontal (BA 10), parietal (BA 7 and BA 40), and occipital (BA 18) activation than typically developing participants. The red minus green trial contrast was further explored by examining activation following green and red cues separately. Individuals with ASDs and typical development showed a similar level of activation to green cues. However, individuals with ASDs exhibited less activation on red trials across most of the same regions found during the between group analysis. This suggests that the ASD group's failure to increase activation following cues indicating the need to engage cognitive control processes is driving the results of the red minus green subtraction, and that group differences are not due solely to an absence of activation across both trial types in the ASD group, but were the result of performance on the more difficult red trials.

In support of the second hypothesis, both the time series and the beta series correlation methods illustrated reduced functional connectivity between frontal and parietal regions in the ASD group. For red trials, the time series correlation method showed reduced connectivity between anterior frontal and visual areas. During green trials, there were also reductions in connectivity between DLPFC

Table 8
Beta series correlation regions for red trials during the cue phase in the group comparision ($n = 45$) when BA 10L is used as the seed. Statistical values were produced from SPM using FDR = 0.05 and k = 10. Only trials in which the subject responded correctly were used.

Region*	Cluster size	Voxel p-value FDR-corrected	Voxel p-value Uncorrected	Approximate Talairach coordinates**		
				x	y	z
Controls versus patients						
LH Postcentral Gyrus (BA 3)	4442	0.050	0.000	−20	−25	47
RH Inferior Parietal Lobule (BA 39)	121	0.050	0.000	44	−66	42
RH Hippocampus	1245	0.050	0.000	28	−22	−6
LH Superior Temporal Gyrus (BA 38)	142	0.050	0.000	−38	16	−26
RH Superior Frontal Gyrus (BA 8)	107	0.050	0.000	10	30	48
LH Thalamus	40	0.050	0.000	−6	−21	14
LH Middle Temporal Gyrus (BA 21)	228	0.050	0.000	−55	−48	6
LH Fusiform Gyrus (BA 37)	61	0.050	0.000	−38	−53	−12
LH Superior Frontal Gyrus (BA 6)	405	0.050	0.000	−2	17	58
LH Superior Frontal Gyrus (BA 10)	30	0.050	0.000	−24	52	−4
RH Posterior Cingulate(BA 23)	31	0.050	0.000	10	−40	24
LH Middle Frontal Gyrus (BA 6)	106	0.050	0.000	−30	−11	48
LH Caudate Body	13	0.050	0.000	−10	15	21
RH Supramarginal Gyrus (BA 40)	35	0.050	0.000	59	−46	19
RH Posterior Cingulate (BA 30)	47	0.050	0.001	12	−62	10
RH Cerebellar Tonsil	12	0.050	0.001	32	−43	−35
LH Culmen	27	0.050	0.001	−10	−55	−2
RH Postcentral Gyrus (BA 7)	31	0.050	0.001	16	−53	65
RH Inferior Parietal Lobule (BA 40)	52	0.050	0.001	44	−33	46
RH Lateral Posterior Nucleus	37	0.050	0.001	18	−19	14
LH Superior Temporal Gyrus (BA 22)	30	0.050	0.001	−46	−31	2
LH Amygdala	16	0.050	0.001	−28	−7	−18
RH Postcentral Gyrus (BA 3)	15	0.050	0.001	18	−39	72
LH Cingulate Gyrus (BA 32)	16	0.050	0.001	−22	4	33
LH Parahippocampal Gyrus (BA 27)	16	0.050	0.001	−26	−27	−4
RH Lingual Gyrus (BA 18)	12	0.050	0.001	24	−56	3
LH Caudate Body	12	0.050	0.001	−16	−1	24
LH Inferior Parietal Lobule (BA 40)	18	0.050	0.001	−51	−50	41
RH Precuneus (BA 7)	12	0.050	0.001	20	−62	38
LH Inferior Parietal Lobule (BA 40)	27	0.050	0.001	−36	−40	50
LH Middle Frontal Gyrus (BA 9)	18	0.050	0.001	−36	27	35
RH Superior Parietal Lobule (BA 7)	12	0.050	0.001	32	−47	65

* Regions were defined by using Talairach Daemon and the "Nearest gray Matter" option (Lancaster et al., 2000).
** Approximate Talairach coordinates were derived by using a Matlab function written by Matthew Brett (http://www.imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/mni2tal.m) to convert the MNI coordinates given by SPM.

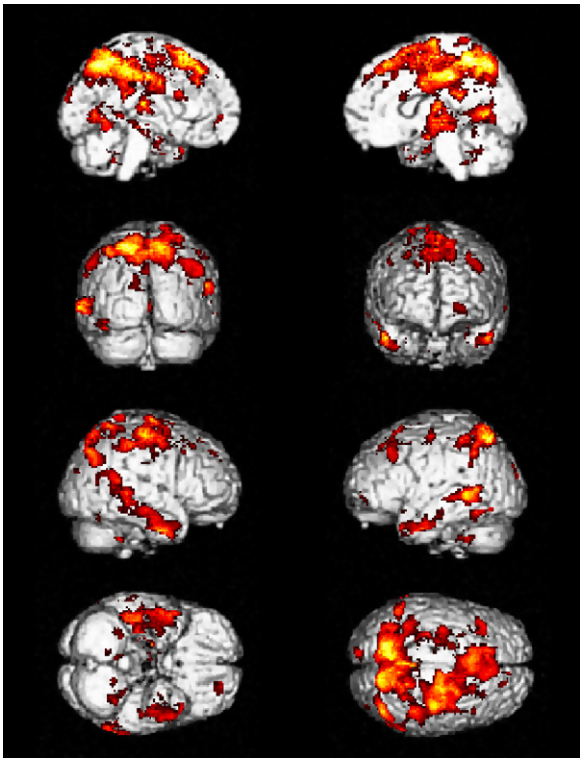

Fig. 3. Renderings of beta series correlation regions for red trials during the cue for the between group comparison $n = 45$, control patients, when BA 10L is the seed.

and anterior PFC and premotor, parietal, cingulate and occipital regions. A factor analysis illustrated that, for the typically developing group during red trials, all brain regions activated on a similar time course. The ASD group, however, exhibited less regional integration during red cue trials with visual and superior parietal regions acting independently of the frontal, cingulate, and inferior parietal regions. The beta series method provided additional evidence of an impairment in fronto-parietal connectivity, as individuals with ASD exhibited reduced connectivity between the

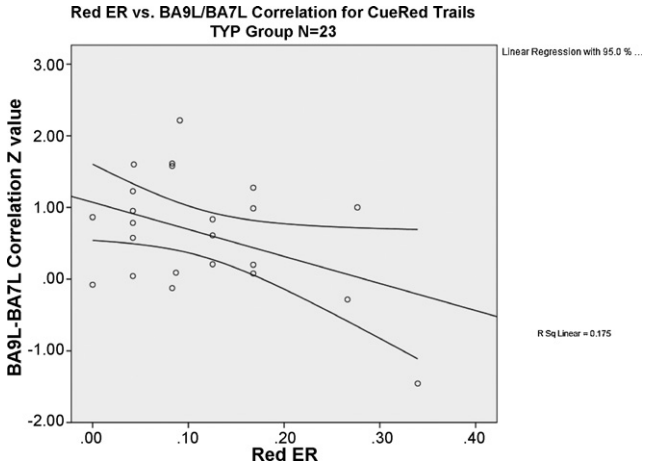

Fig. 4. Scatter plots of red error rates versus the correlation coefficient between BA 9L and BA 7L for the typical group ($n = 23$).

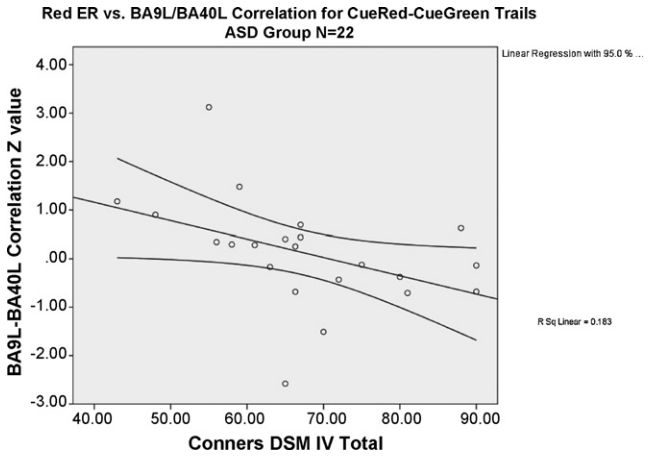

Fig. 5. Scatter plots of Conners' DSM-IV total versus the correlation coefficient between BA 9L and BA 40L for the patient group ($n = 22$).

left anterior PFC and parietal, and visual areas. This analysis also revealed deficits between prefrontal, striatal, and medial temporal areas.

Task performance (red error rates) in typically developing individuals was related to fronto-parietal connectivity. In individuals with ASD, there were modest positive relationships between functional connectivity between prefrontal and visual areas and speeded responding, however these correlations did not survive correction for multiple comparisons. It bears mention that there now have been several findings of speeded responding on correct trials in individuals with ASDs (Bogte, Flamma, Meere, & Engeland, 2007; Thakkar et al., 2008), as well as several findings of general response slowing in individuals with ASDs (Guerts, Verté, Oosterlaan, Roeyers, & Sergeant, 2004; Johnson et al., 2007). Given these contradictions in the literature, studies investigating and comparing speed accuracy tradeoffs and the mechanics of trial-to-trial performance adjustment in different paradigms could help advance our understanding of cognitive control in ASDs.

As hypothesized, fronto-parietal connectivity was inversely related to ADHD symptoms. Like children with ADHD, children with ASDs demonstrated greater response inhibition deficits when external cues were unavailable for use over the long delay period involved in this task. However, while they may show response inhibition deficits in some cases (e.g. Guerts et al., 2004; Solomon et al., 2008), children with ASDs may not exhibit these difficulties when prepotency is not sufficiently strong, or when they do not have clinically significant attention symptoms, and these alternatives should be examined more systematically in future studies.

Our findings add to the recent consensus that ASDs involve fronto-parietal connectivity deficits (Just et al., 2007; Kana et al., 2007). How might these deficits affect functioning in individuals with ASDs? Parietal cortex has been implicated in storage of spatial information in working memory (Funahashi, Chafee, & Goldman-Rakic, 1993; Wager & Smith, 2003), and is sensitive to both rule representation and generally is active when there is a need to control task sets (Brass & von Cramon, 2002; Bunge, 2004; Crone, Wendelken, Donohue, & Bunge, 2006). Anterior frontal activation in BA (10) has been associated with a wide range of functions including switching of attention between percepts (Pollman, 2001), subgoal processing (Braver & Bongiolatti, 2002), maintaining higher order and/or abstract mental representations of task contingencies (Badre, 2008; Badre & D'Esposito, 2007; Botvinick, 2008; Frank & O'Reilly, 2006; Koechlin, Ody, & Kouneiher, 2003), regulating stimulus-oriented versus stimulus-independent processing (Burgess, Dumontheil, & Gilbert, 2007), and preserving a dynamic balance between controlled and rapid automatic responding (Braver et al., 2003; Brown, Reynolds, & Braver, 2007). The combination of difficulties in maintaining the task set online, coupled with the inability to retrieve the appropriate rule accords well with the nature of ASD symptoms. An interesting potential line of inquiry is that deficits in the functioning of anterior prefrontal regions could be involved in the pattern of "missing the forest for the trees" or weak central coherence evident in persons with autism. Indeed, several recent studies have raised this possibility (Gilbert, Bird, Brindley, Frith, & Burgess, 2008; Hill & Bird, 2006).

In this study, we did not find ACC activation in either group during the probe phase of the task. Existing behavioral studies suggest that individuals with ASDs exhibit impairments in cognitive control that persist at least until adulthood (Luna, Doll, Hegedus, Minshew, & Sweeney, 2007; Solomon et al., 2008). Frontal and parietal regions are thought to develop throughout adolescence and early adulthood (Luciana, Conklin, Hooper, & Yarger, 2005; Luna, Garver, Urban, Lazar, & Sweeney, 2004). However, the ACC may exhibit a more delayed developmental trajectory. For example, Velanova, Wheeler, and Luna (2008) showed increased activation of the ACC on error versus correct trials in an antisaccade task with development, with peak neural activation onsets occurring later in adults versus children. They suggest that children and adolescents may receive less feedback to guide future performance. A similar argument has been made by Ladouceur, Dahl, & Carter (2004, 2007), in a study that examined the development of electrophysiological measures of ACC functioning. These findings may help explain why we did not find significant and expected probed period ACC activation in either typically developing adolescents or those with ASDs, and underscore the great need for additional developmental neuroimaging studies.

Potential limitations of the current study should be discussed. First, we elected to include the 55% of subjects with clinically significant symptoms of ADHD. As we have argued previously (Solomon et al., 2008), co-morbid attention problems are likely part of the autism phenotype, and to exclude such children would preclude us from learning important information about the population as a whole. On the other hand, future studies should look at groups of children with ASDs with and without co-morbid ADHD symptoms to isolate potential differences. Second, we elected to include participants taking SSRIs in the ASD group, given the high percentage of these children taking these medications. Unlike stimulant medications which wash out quickly, SSRIs would require several weeks, and we could not justify taking this approach in children benefiting from this therapy targeting social anxiety and/or depression. Finally, the POP task is relatively long, and we lost 30% of subjects due to excess motion. Although participants with excess motion came from both groups equally, future studies of cognitive control in ASDs should use briefer tasks in an attempt to reduce the risk that findings are an artifact of a non-representative sample.

In summation, this study provides additional evidence of cognitive control deficits and the first evidence of fronto-parietal connectivity deficits in adolescents with ASDs. We also documented a relationship between reduced fronto-parietal connectivity and ADHD symptoms in individuals with ASDs. Future studies should examine the relationship between these deficits further in an attempt to shed light on issues related to co-morbidity, and the pathophysiology of neurodevelopmental disorders in general.

References

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed. Text Revised). Washington, DC: American Psychiatric Association.

Badre. (2008). Cognitive control, hierarchy, and the rostro-caudal organization of the frontal lobes. *Trends in Cognitive Sciences*, *12*(5), 193–200.

Badre, & D'Esposito. (2007). Functional magnetic resonance imaging evidence for a hierarchical organization of the prefrontal cortex. *Journal of Cognitive Neuroscience*, *19*(12), 2082–2099.

Barber, A. D., & Carter, C. S. (2005). Cognitive control involved in overcoming prepotent response tendencies and switching between tasks. *Cerebral Cortex*, *15*(7), 899–912.

Belmonte, M. K., & Yurgelun-Todd, D. A. (2003). Functional anatomy of impaired selective attention and compensatory processing in autism. *Cognitive Brain Research*, *17*(3), 651–664.

Berument, S. K., Rutter, M., Lord, C., Pickles, A., & Bailey, A. (1999). Autism screening questionnaire: Diagnostic validity. *British Journal of Psychiatry*, *175*, 444–451.

Bogte, H., Flamma, B., Meere, J. v., & Engeland, d. H. v. (2007). Post-error adaptation in adults with high functioning autism. *Neuropsychologia*, *45*(8), 1707–1714.

Booth, J., Burman, D., Meyer, J. R., Lei, Z., Trommer, B. L., Davenport, N. D., et al. (2005). Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *46*(1), 94–111.

Botvinick, M. M. (2008). Hierarchical models of behavior and prefrontal function. *Trends in Cognitive Sciences*, *12*(5), 201–208.

Botvinick, M. M., Cohen, J. D., & Carter, C. S. (2004). Conflict monitoring and anterior cingulate cortex: An update. *Trends in Cognitive Sciences*, *8*(12), 539–546.

Brass, M., & von Cramon, D. Y. (2002). The role of the frontal cortex in task preparation. *Cerebral Cortex*, *12*(9), 908–914.

Braver, T. S., & Bongiolatti, S. R. (2002). The role of frontopolar cortex in subgoal processing during working memory. *NeuroImage*, *14*(3), 523–536.

Braver, T. S., Cohen, D. J., & Barch, D. M. (2002). *The role of prefrontal cortex in normal and disordered cognitive control: A cognitive neuroscience perspective*. New York: Oxford University Press.

Braver, T. S., Reynolds, J. R., & Donaldson, D. I. (2003). Neural mechanisms of transient and sustained cognitive control during task switching. *Neuron*, *39*(4), 713–726.

Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002). Region of interest analysis using an SPM toolbox. In *Presented at the 8th international conference on functional mapping of the human brain* June 2–6,

Brieber, S., Neufang, S., Bruning, N., Kamp-Becker, I., Remschmidt, H., Herpertz-Dahlmann, B., et al. (2007). Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *48*, 1251–1258.

Brown, J. W., Reynolds, J. R., & Braver, T. S. (2007). A computational model of fractionated conflict-control mechanisms in task-switching. *Cognitive Psychology*, *55*(1), 37–85.

Bunge, S. A. (2004). How we use rules to select actions: A review of evidence from cognitive neuroscience. *Cognitive, Affective, & Behavioral Neuroscience*, *4*, 564–579.

Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., & Gabrieli, J. D. E. (2002). Immature frontal lobe contributions to cognitive control in children: Evidence from fMRI. *Neuron*, *33*(2), 301–311.

Bunge, S. A., Kahn, I., Wallis, J. D., Miller, E. K., & Wagner, A. D. (2003). Neural circuits subserving the retrieval and maintenance of abstract rules. *Journal of Neurophysiology*, *90*(5), 3419–3428.

Burgess, P. W., Dumontheil, I., & Gilbert, S. J. (2007). The gateway hypothesis of rostral prefrontal cortex (area 10) function. *Trends in Cognitive Sciences*, *11*, 290–298.

Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D., & Cohen, J. D. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, *280*(*5364*), 747–749.

Carter, C. S., & Pine, D. S. (2006). Polishing the windows of the mind. *The American Journal of Psychiatry*, *163*(5), 761–763.

Casey, B. J., Nigg, J. T., & Durston, S. (2007). New potential leads in the biology and treatment of attention deficit-hyperactivity disorder. *Current Opinion in Neurology*, *20*, 119–124.

Center for Disease Control and Prevention. Prevalence of Autism Spectrum Disorders- Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2002. Surveillance Summaries, 2007. MMWR 2007; 56. (No. SS-1).

Conners, C. K., Sitarenios, G., Parker, J. D. A., & Epstein, J. N. (1998). The revised Conners' Parent Rating Scale (CPRS-R): Factor structure, reliability, and criterion. *Journal of Abnormal Child Psychology*, *26*(4), 257–268.

Corbetta, M., Kincade, J. M., Ollinger, J. M., McAvoy, M. P., & Shulman, G. L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nature Neuroscience*, *3*, 292–297.

Crone, E., Wendelken, C., Donohue, S., & Bunge, S. (2006). Neural evidence for dissociable components of task-switching. *Cerebral Cortex*, *16*(4), 475–486.

Curtis, C., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences*, *7*(9), 415–423.

Curtis, C., Rao, V., & D'Esposito, M. (2004). Maintenance of spatial and motor codes during oculomotor delayed response tasks. *The Journal of Neuroscience*, *24*(16), 3944–3952.

D'Esposito, M., & Postle, B. R. (2002). The organization of working memory function in lateral prefrontal cortex: Evidence from event-related functional MRI. In *Principles of frontal lobe function* (pp. 168–187).

Dickstein, S., Bannon, K., Castellanos, F., & Milham, M. (2006). The neural correlates of attention deficit hyperactivity disorder: An ALE meta-analysis. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *47*(10), 1051–1062.

Dreher, J., Koechlin, E., Ali, S., & Grafman, J. (2002). The roles of timing and task order during task switching. *NeuroImage*, *17*(1), 95–109.

Durston, S., Tottenham, N., Thomas, K., Davidson, M., Eigsti, I., Yang, Y., et al. (2003). Differential patterns of striatal activation in young children with and without ADHD. *Biological Psychiatry*, *53*(10), 871–878.

Egner, T., & Hirsch, J. (2005). Cognitive control mechanisms resolve conflict through cortical amplification of task-relevant information. *Nature Neuroscience*, *8*(12), 1784–1790.

Frank, M., & O'reilly, R. (2006). A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. *Behavioral neuroscience*, *120*(3), 497–517.

Funahashi, S., Chafee, M., & Goldman-Rakic, P. (1993). Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature*, *365*(6448), 753–756.

Fuster, J. M. (2002). Frontal lobe and cognitive development. *Journal of Neurocytology*, *31*(3–5), 373–385.

Genovese, C. R., Lazar, N. A., & Nichols, T. E. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage*, *15*, 870–878.

Gilbert, S. J., Bird, G., Brindley, R., Frith, C. D., & Burgess, P. W. (2008). Atypical recruitment of medial prefrontal cortex in autism spectrum disorders: An fMRI study of two executive function tasks. *Neuropsychologia*, *46*(9), 2281–2291.

Guerts, H. M., Verté, S., Oosterlaan, J., Roeyers, H., & Sergeant, J. A. (2004). How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? *Journal of Child Psychology and Psychiatry*, *45*, 836–854.

Haist, F., Adamo, M., Westerfield, M., Courchesne, E., & Townsend, J. (2005). The functional neuroanatomy of spatial attention in autism spectrum disorder. *Developmental Neuropsychology*, *27*(3), 425–458.

Hill, E. L., & Bird, C. M. (2006). Executive processes in Asperger syndrome: Patterns of performance in a multiple case series. *Neuropsychologia*, *44*(14), 2822–2835.

Howlin, P. (2003). Outcome in high-functioning adults with autism with and without early language delays: Implications for the differentiation between autism and Asperger's Disorder. *Journal of Autism and Developmental Disorders*, *33*(1), 3–13.

Johnson, K. A., Robertson, I. H., Kelly, S. P., Silk, T. J., Barry, E., Dáibhis, A., et al. (2007). Dissociation in performance of children with ADHD and high-functioning autism on a task of sustained attention. *Neuropsychologia*, *11*, 2234–2245.

Just, M., Cherkassky, V., Keller, T., & Minshew, N. (2004). Cortical activation and synchronization during sentence comprehension in high-functioning autism: Evidence of underconnectivity. *Brain*, *127*, 1811–1821.

Just, M., Cherkassky, V., Keller, T., Kana, R., & Minshew, N. (2007). Functional and anatomical cortical underconnectivity in autism: Evidence from an FMRI study of an executive function task and corpus callosum morphometry. *Cerebral Cortex*, *17*, 951–961.

Kana, R. K., Keller, T. A., Minshew, N. J., & Just, M. A. (2007). Inhibitory control in high-functioning autism: Decreased activation and underconnectivity in inhibition networks. *Biological Psychiatry*, *62*(3), 198–206.

Kerns, J. G. (2006). Anterior cingulate and prefrontal cortex activity in an FMRI study of trial-to-trial adjustments on the Simon task. *NeuroImage*, *33*(1), 399–405.

Koechlin, E., Ody, C., & Kouneiher, F. (2003). The architecture of cognitive control in the human prefrontal cortex. *Science*, *302*(5648), 1181–1185.

Koshino, H., Carpenter, P. A., Minshew, N. J., Cherkassky, V. L., Keller, T. A., & Just, M. A. (2005). Functional connectivity in a fMRI working memory task in high-functioning autism. *NeuroImage*, *24*(3), 810–821.

Ladouceur, C. D., Dahl, R. E., & Carter, C. S. (2004). ERP correlates of action monitoring in adolescence. *Annals of the New York Academy of Sciences*, *1021*, 329–336.

Ladouceur, C. D., Dahl, R. E., & Carter, C. S. (2007). Development of action monitoring through adolescence into adulthood: ERP and source localization. *Developmental Science*, *10*(6), 874–891.

Lancaster, J. L., Summerlin, J. L., Rainey, L., Freitas, C. S., & Fox, P. T. (1997). The Talairach Daemon, a database server for Talairach Atlas Labels. *NeuroImage*, *5*, S633.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., et al. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping*, *10*(3), 120–131.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Leventhal, B. L., & DiLavore, P. C. (2000). The Autism Diagnostic Observation Schedule-Generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders*, *30*(3), 205–223.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *24*(5), 659–685.

Luciana, M., Conklin, H. M., Hooper, C. J., & Yarger, R. S. (2005). The development of nonverbal working memory and executive control processes in adolescents. *Child Development*, *76*(3), 697–712.

Luna, B., Doll, S. K., Hegedus, S. J., Minshew, N. J., & Sweeney, J. A. (2007). Maturation of executive function in autism. *Biological Psychiatry*, *61*(4), 474–481.

Luna, B., Garver, K. E., Urban, T. A., Lazar, N. A., & Sweeney, J. A. (2004). Maturation of cognitive processes from late childhood to adulthood. *Child Development*, *75*(5), 1357–1372.

Luna, B., Minshew, N. J., Garver, B. A., Lazar, N. A., Thulborn, K. R., Eddy, W. F., et al. (2002). Neocortical system abnormalities in autism: An fMRI study of spatial working memory. *Neurology*, *59*(6), 834–840.

MacDonald, A. W., Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, *288*(5472), 1835–1838.

Macintosh, K. E., & Dissanayake, C. (2004). Annotation: The similarities and differences between autistic disorder and Asperger's disorder: A review of the empirical evidence. *Journal of Child Psychology and Psychiatry*, *45*(3), 421–434.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fmri data sets. *NeuroImage*, *19*, 1233–1239 (WFU Pickatlas, version 1232.1234).

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202.

Minshew, N. J., & Williams, D. L. (2007). The new neurobiology of autism: Cortex, connectivity, and neuronal organization. *Archives of Neurology*, *64*(7), 945–950.

Nigg, J. T., & Casey, B. J. (2005). An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. *Developmental Psychopathology*, *17*(3), 785–806.

Nyden, A., Hjelmquist, E., & Gillberg, C. (2000). Autism spectrum and attention-deficit disorders in girls. Some neuropsychological aspects. *European Child and Adolescent Psychiatry*, *9*(3), 180–185.

Ozonoff, S., & Griffith, E. M. (2000). Neuropsychological function and the external validity of Asperger's Disorder. In A. Klin, F. R. Volkmar, & S. S. Sparrow (Eds.), *Asperger's Disorder* (p. 24). New York: Guilford Press.

Ozonoff, S., Pennington, B. F., & Solomon, M. (2006). Neuropsychological perspectives on developmental psychopathology. In D. Cicchetti, & D. J. Cohen (Eds.), *Developmental psychopathology: Developmental neuroscience* (pp. 332–380). New Jersey: John Wiley & Sons, Inc.

Perlstein, W. M., Dixit, N. K., Carter, C. S., Noll, D. C., & Cohen, J. D. (2003). Prefrontal cortex dysfunction mediates deficits in working memory and prepotent responding in schizophrenia. *Biological Psychiatry*, *53*(1), 25–38.

Peterson, B. S., Skudlarski, P., Gatenby, J. C., Zhang, H., Anderson, A. W., & Gore, J. C. (1999). An fMRI study of Stroop word-color interference: evidence for cingulate subregions subserving multiple distributed attentional systems. *Society of Biological Psychiatry*, *45*, 1237–1258.

Pollman, S. (2001). Switching between dimensions, location, and responses: The role of the left frontopolar cortex. *NeuroImage*, *14*, 118–124.

Ravizza, S. M., & Carter, C. S. (2008). Shifting set about task switching: Behavioral and neural evidence for distinct forms of cognitive flexibility. *Neuropsychologia*, *46*(12), 2924–2935.

Rissman, J., Gazzaley, A., & D'Esposito, M. (2004). Measuring functional connectivity during distinct stages of a cognitive task. *NeuroImage*, *23*(2), 752–763.

Rosano, C., Aizenstein, H., Cochran, J., Saxton, J., De Kosky, S., Newman, A. B., et al. (2005). Functional neuroimaging indicators of successful executive control in the oldest old. *NeuroImage*, *28*(4), 881–889.

Rutter, M., Bailey, A., & Lord, C. (2003). *SCQ: Social communication questionnaire*. Los Angeles, CA: Western Psychological Services.

Rypma, B., Berger, J. S., & D'Esposito, M. (2002). The influence of working-memory demand and subject performance on prefrontal cortical activity. *Journal of Cognitive Neuroscience*, *14*(5), 721–731.

Schmitz, N., Rubia, K., Daly, E., Smith, A., Williams, S., & Murphy, D. G. M. (2006). Neural correlates of executive function in autistic spectrum disorders. *Biological Psychiatry*, *59*(1), 7–16.

Shafritz, K., Dichter, G., Baranek, G., & Belger, A. (2008). The neural circuitry mediating shifts in behavioral response and cognitive set in autism. *Biological Psychiatry*, *63*(10), 974–980.

Silk, T. J., Rinehart, N., Bradshaw, J., Tonge, B., Egan, G., O'Boyle, M. W., & Cunnington, R. (2006). Visuospatial processing and the function of prefrontal-parietal networks in autism spectrum disorders: A functional MRI study. *American Journal of Psychiatry*, *163*, 1440–1443.

Snitz, B. E., MacDonald, A., III, Cohen, J. D., Cho, R. Y., Becker, T., & Carter, C. S. (2005). Lateral and medial hypofrontality in first-episode schizophrenia: functional activity in a medication-naive state and effects of short-term atypical antipsychotic treatment. *American Journal of Psychiatry*, *162*, 2322–2329.

Solomon, M., Ozonoff, S. J., Cummings, N., & Carter, C. S. (2008). Cognitive control in autism spectrum disorder. *International Journal of Developmental Neuroscience*, *26*(2), 239–247.

Szatmari, P., Bryson, S. E., Boyle, M. H., Streiner, D. L., & Duku, E. (2003). Predictors of outcome among high functioning children with autism and Asperger's Disorder. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *44*(4), 520–528.

Takarae, Y., Minshew, N. J., Luna, B., & Sweeney, J. A. (2007). Atypical involvement of frontostriatal systems during sensorimotor control in autism. *Psychiatry Research: Neuroimaging*, *156*(2), 117–127.

Thakkar, K. N., Polli, F. E., Joseph, R. M., Tuch, D. S., Hadjikhani, N., Barton, J. J., et al. (2008). Response monitoring, repetitive behaviour and anterior cingulate abnormalities in ASD. *Brain*, *131*(9), 2464–2478.

Thompson-Schill, S. L., Bedny, M., & Goldberg, R. F. (2005). The frontal lobes and the regulation of mental activity. *Current Opinion in Neurobiology*, *15*(2), 219–224.

Velanova, K., Wheeler, M., & Luna, B. (2008). Maturational changes in anterior cingulate and frontoparietal recruitment support the development of error processing and inhibitory control. *Cerebral Cortex*, *18*(11), 2505–2522.

Verté, S., Geurts, H., Roeyers, H., Oosterlaan, J., & Sergeant, J. (2006). Executive functioning in children with an Autism Spectrum Disorder: Can we differentiate within the spectrum? *Journal of Autism and Developmental Disorders*, *36*(3), 351–372.

Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: A meta-analysis. *Cognitive, Affective, & Behavioral Neuroscience*, *3*(4), 255–274.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence (WASI)*. San Antonio: Harcourt Assessment.

Wendelken, C., Bunge, S. A., & Carter, C. S. (2008). Maintaining structured information: An investigation into functions of parietal and lateral prefrontal cortices. *Neuropsychologia*, *46*(2), 665–678.

Yarkoni, T., Gray, J. R., Chrastil, E. R., Barch, D. M., Green, L., & Braver, T. S. (2005). Sustained neural activity associated with cognitive control during temporally extended decision making. *Cognitive Brain Research*, *23*(1), 71–84.

Yeung, N., Nystrom, L. E., Aronson, J. A., & Cohen, J. D. (2006). Between-task competition and cognitive control in task switching. *Journal of Neuroscience*, *26*(5), 1429–1438.