Inhibitory Control in High-Functioning Autism: Decreased Activation and Underconnectivity in Inhibition Networks

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Background: Inhibiting prepotent responses is critical to optimal cognitive and behavioral function across many domains. Several behavioral studies have investigated response inhibition in autism, and the findings varied according to the components involved in inhibition. There has been only one published functional magnetic resonance imaging (fMRI) study so far on inhibition in autism, which found greater activation in participants with autism than control participants.

Methods: This study investigated the neural basis of response inhibition in 12 high-functioning adults with autism and 12 age- and intelligence quotient (IQ)-matched control participants during a simple response inhibition task and an inhibition task involving working memory.

Results: In both inhibition tasks, the participants with autism showed less brain activation than control participants in areas often found to be active in response inhibition tasks, namely the anterior cingulate cortex. In the more demanding inhibition condition, involving working memory, the participants with autism showed more activation than control participants in the premotor areas. In addition to the activation differences, the participants with autism showed lower levels of synchronization between the inhibition network (anterior cingulate gyrus, middle cingulate gyrus, and insula) and the right middle and inferior frontal and right inferior parietal regions.

Conclusions: The results indicate that the inhibition circuitry in the autism group is activated atypically and is less synchronized, leaving inhibition to be accomplished by strategic control rather than automatically. At the behavioral level, there was no difference between the groups.

Key Words: Autism, factor analysis, fMRI, functional connectivity, inhibitory control, response inhibition, underconnectivity

Response inhibition is a key executive control process that helps govern complex cognition and in turn complex adaptive behavior. When response inhibition is functioning properly its contributions are not visible, because a successfully inhibited response simply does not emerge, at least not behaviorally. In autism, several types of behavior are commonly observed that are suggestive of malfunctioning of response inhibition processes. The inability to inhibit context-inappropriate behavior is typical of autism and often leads to actions and verbalizations that are inappropriate in timing or to the circumstances. Even when aware of the need to not respond, people with autism may be unable to suppress an inappropriate behavior. This circumstance leads to socially embarrassing incidents for parents and at times to serious legal consequences. Neuropsychologic tests have reported variable results with regard to performance on tests of inhibition in autism.

Some studies of response inhibition have indicated that high-functioning individuals with autism are not impaired at inhibiting simple responses, such as pressing a button for circles but not for squares (Bishop and Norbury 2005; Goldberg *et al.* 2005; Kleinhans *et al.* 2005; Ozonoff and Strayer 1997; Ozonoff *et al.* 1994). Several paradigms have shown no impairments in people with autism in response inhibition, such as Stroop tasks (Eskes *et al.* 1990; Ozonoff and Jensen 1999; Schmitz *et al.* 2006), "go-no-go" tasks (Schmitz *et al.* 2006), simple inhibition in "go-no-go" tasks (Ozonoff and Strayer 1997; Ozonoff *et al.* 1994), stop-signal tasks (Ozonoff and Strayer 1997), negative priming tasks (Brian *et al.* 2003; Ozonoff and Strayer 1997), and switch tasks (Schmitz *et al.* 2006). All these paradigms have simple inhibition as the common factor. However, people with autism have difficulty in tasks that impose a working memory load in addition to requiring response inhibition (Hughes 1996; Hughes and Russell 1993; Minshew *et al.* 1999; Russell 1997) or when they are required to shift from one response set to another (Ozonoff and Strayer 1997; Ozonoff *et al.* 1994). Paradigms such as memory-based eye movement inhibition tasks (Goldberg *et al.* 2002, 2005; Luna *et al.* 2006; Minshew *et al.* 1999), the set shifting component of "go-no-go" tasks (Ozonoff and Strayer 1997; Ozonoff *et al.* 1994), and NEPSY Knock-Tap tasks (Korkman *et al.* 1998) that tap working memory and inhibitory control (Joseph *et al.* 2005) have shown impairments in performance in autism. Thus, behavioral studies indicate that the inhibition impairments in autism are not ubiquitous but depend on the nature, complexity, and subdomains of the task at hand. The functional magnetic resonance imaging (fMRI) study reported here offers the possibility of determining the neural basis of the inhibition impairment. The study investigated the brain activation and synchronization in autism in a simple response inhibition task as well as in a 1-back inhibition task.

It is important to recognize that response inhibition and working memory are functions that do not occur in isolation but whose expression occurs in the context of some task. For example, in normal participants, the size of a working memory load affects the ability to suppress inappropriate responses (Roberts *et al.* 1994; Conway *et al.* 1999). Moreover, response inhibition must be carefully coordinated with other facets of processing, so that just the right response is inhibited at just the right time. A theory of cortical underconnectivity in autism (Just *et al.* 2004) would suggest that the coordinated nature of response inhibition (requiring communication among the neural centers underpinning a task) might be particularly susceptible to disruption in autism. In particular, intact

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neuronal connectivity is essential for the ability to exert top-down control that allows voluntary response suppression. Investigating response inhibition from an underconnectivity perspective places a focus not only on the regions found to be involved in accomplishing inhibition but also on the coordination among various regions and networks.

The study used a "go-no-go" paradigm, which requires the participants to respond on "go" trials and to inhibit their response on "no-go" trials. Cortical circuits involving diverse areas of frontal cortex and other association cortex sites such as parietal cortex are implicated in the inhibition of responses during "no-go" trials in a "go-no-go" task (Liddle *et al.* 2001). Brain imaging studies have also found the anterior cingulate cortex to be involved in the detection of conflict between competing responses (Botvinick *et al.* 2001; Carter *et al.* 1998) and in monitoring for the occurrence of response conflict in information processing (Barch *et al.* 2000; Botvinick *et al.* 1999, 2001; Braver *et al.* 2001; Carter *et al.* 1998; Carter *et al.* 2000). Such findings also suggest that the anterior cingulate would be particularly active during "no-go" events.

Atypical activation in cingulate cortex in autism has been found in several studies. For instance, Gomot *et al.* (2006) found reduced activation in left anterior cingulate gyrus in autism during auditory detection of acoustic deviance and novelty. Luna *et al.* (2002) found reduced activation in autism in posterior cingulate cortex in a spatial working memory task. Studies have also suggested that atypical preparation in motor planning tasks in autism is consistent with a disturbance of functions in the supplementary motor cortex and the anterior cingulate (Rinehart *et al.* 2001). The results from these studies suggest impairments in autism related to cingulate cortex functioning. Some of these functions include monitoring one's performance from time to time and detecting any errors that are made. In addition to considerations of cortical function, differences in brain structure also enter into accounts of autism. Converging evidence from magnetic resonance imaging (MRI)-based morphometry (Abell *et al.* 1999; Haznedar *et al.* 2000), diffusion tensor imaging (DTI) (Barnea-Goraly *et al.* 2004), positron-emission tomography (PET) (Haznedar *et al.* 1997, 2000), single-photon emission computed tomography (SPECT) (Ohnishi *et al.* 2000), and postmortem studies (Bauman and Kemper 1994) have indicated abnormalities associated with cingulate cortex in autism.

Response inhibition is a process that needs a good amount of cognitive control and it involves preparing for responding, monitoring performance, and detecting errors. This is accomplished by the coordination of regions like cingulate cortex and other frontal and parietal regions. Based on the previous findings in autism, we hypothesized that participants with autism would show reduced activation in cingulate regions compared with control participants. We also hypothesized that the participants with autism would exhibit lower levels of synchronization of the inhibition network (involving cingulate regions and insula) with frontal and parietal regions. At the behavioral level, we hypothesized that the autism group would show more inhibition-related errors than the control participants in the 1-back inhibition task but not in the simple inhibition task.

Methods and Materials

Participants

Twelve high-functioning individuals with autism (mean age 26.8 years) and twelve control participants (mean age 22.5 years) were included in the analyses (Full Scale and Verbal IQ scores of 80 or above based on the Wechsler Abbreviated Scale of Intelligence [WASI]) (Wechsler 1999). Participants were matched on the basis of age and intelligence quotient (IQ) (Table 1). The diagnosis of autism was established using two structured research diagnostic instruments, the Autism Diagnostic Interview-Revised (ADI-R) (Lord *et al.* 1994) and the Autism Diagnostic Observation Schedule-Generic (ADOS-G) (Lord *et al.* 2000), supplemented with confirmation by expert clinical opinion. Potential participants with autism were excluded on the basis of an associated disorder, such as fragile-X syndrome or tuberous sclerosis. Potential control participants and participants with autism were also excluded if found to have evidence of birth asphyxia, head injury, or a seizure disorder. Exclusionary criteria were based on history, examination, and chromosomal analysis.

Table 1. Age, IQ, Handedness, and Gender of Participants

Measure	Autism	Control
Age (Years)		
Mean ± SD	26.8 ± 7.7	22.5 ± 3.2
VIQ		
Mean ± SD	110.1 ± 14.4	114.0 ± 10.0
PIQ		
Mean ± SD	107.1 ± 13.8	116.9 ± 6.4
FSIQ		
Mean ± SD	110.1 ± 12.6	117.0 ± 8.7
Handedness		
Right : left	11 : 1	11 : 1
Gender		
Male : female	11 : 1	11 : 1

IQ, intelligence quotient; VIQ, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient; FSIQ, Full-Scale Intelligence Quotient.

The control participants were medically healthy community volunteers recruited to match the participants with autism on age, full-scale IQ, gender, race, and family of origin socioeconomic status, as measured by the Hollingshead method. Potential control participants were screened by questionnaire, telephone, face-to-face interview, and observation during psychometric testing to determine eligibility. Exclusionary criteria included current or past psychiatric and neurologic disorders, birth injury, developmental delay, school problems, acquired brain injury, learning disabilities, and medical disorders with implications for the central nervous system or those requiring regular medication. Potential control participants were also screened to exclude those with medical illnesses or a family history of autism; developmental cognitive, affective, or anxiety disorders; schizophrenia; obsessive-compulsive disorder; or other neurologic or psychiatric disorder thought to have a genetic component in first-degree relatives.

Each participant signed an informed consent that had been approved by the University of Pittsburgh and Carnegie Mellon University Institutional Review Boards. Prior to testing in the scanner, each participant was familiarized with the task and had as many opportunities to practice in the MRI simulator as needed for comfort and to attain head motion quality standards.

Experimental Paradigm

This experiment assessed the brain activation and performance in autism and control participants during a response inhibition task. There were three experimental conditions and a fixation baseline condition. In all three experimental conditions, alphabetic characters were displayed one at a time, in the center of the computer screen, at a rate of one every 1000 msec. The participants were instructed to press a button with their index

finger for every letter except for those that met certain criteria. Those criteria for inhibiting the response varied across the three conditions in the experiment.

First, in a baseline condition, participants were instructed to "press for every letter except A"; however, no As were presented here and thus the participant pressed a button for every letter, never requiring any inhibition of a response. The second condition, simple response inhibition, had the same instructions, but in this condition As were presented. Fifteen As were presented per 60-letter run (25% of the time, i.e., on average, once every 4 sec). The third condition, 1-back inhibition, displayed only the letters "F" or "G." The participant was instructed to "press for every letter EXCEPT for the second of two consecutive Fs and/or two consecutive Gs" (Figure 1). As in the previous condition, letters requiring inhibition occurred 15 times per 60-letter run (25% of the time, i.e., on average, once every 4 sec). The inhibition tasks were developed based on two previous studies (Casey *et al.* 1997; Garavan *et al.* 1999).

Each participant practiced the task before going into the scanner. The practice consisted of one 60-letter run of the simple inhibition task and one 60-letter run of the 1-back inhibition task. Participants made all responses using a one-button mouse, held in their right hand. The display of each letter lasted 500 msec, followed by a 500-msec blank interval. A 6-second delay occurred between 60-letter runs. There were two 60-letter runs of each condition (simple inhibition and 1-back inhibition). In addition, a 24-sec fixation baseline was presented after every two 60-letter runs to provide a baseline measure of brain activation with which to compare each experimental condition. In this fixation condition, participants fixated on a centered asterisk without performing any task. In addition, one 60-letter run of a no inhibition task (press button for every letter on the screen) was presented at the beginning, which would provide a baseline for contrast with the inhibition conditions. The order of the conditions was counterbalanced.

Imaging Parameters

The imaging was carried out at the Brain Imaging Research Center (BIRC), University of Pittsburgh and Carnegie Mellon University, on a 3-Tesla Siemens Allegra scanner (Siemens, Erlangen, Germany) using a circularly polarized transmit/receive head coil. The stimuli were rear-projected onto a translucent plastic screen and participants viewed the screen through a mirror attached to the head coil. For the functional imaging, a gradient echo, echo-planar pulse sequence was used with repetition time (TR) = 1000 msec, echo time (TE) = 30 msec, and a flip angle of 60°. Sixteen adjacent oblique axial slices were acquired in an interleaved sequence, with 5-mm slice thickness, 1-mm slice gap, a 20 × 20 cm field of view (FOV), and a 64 × 64 matrix, resulting in an in-plane resolution of 3.125 × 3.125 mm. A 160-slice 3D MPRAGE volume scan with TR = 200 msec, TE = 3.34 msec, flip angle = 7, FOV = 25.6 cm, 256 × 256 matrix size, and 1-mm slice thickness was acquired at the same orientation as the oblique axial functional images for each participant.

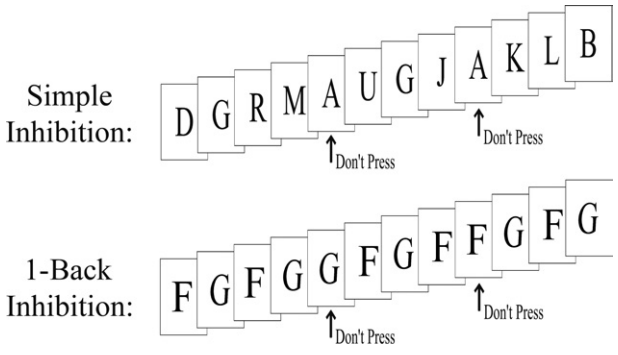

Figure 1. Letter stream stimuli used for the simple response inhibition task and the 1-back response inhibition task.

Distribution of Activation

To compare the participating groups in terms of the distribution of activation, the data were analyzed using SPM99 software (Wellcome Department of Cognitive Neurology, London, United Kingdom). Images were corrected for slice acquisition timing, motion-corrected, normalized to the Montreal Neurological Institute (MNI) template, resampled to 2 × 2 × 2 mm voxels, and smoothed with an 8-mm Gaussian kernel to decrease spatial noise. Statistical analysis was performed on individual and group data by using the general linear model as implemented in SPM99 (Friston *et al.* 1995). Group analyses were performed using a random-effects model. Contrasts reflecting the inhibition effects for each group, group by inhibition interactions, and the group differences in the distribution of activation relative to fixation were computed. For the group difference contrasts, possible differences in deactivation (relative to fixation condition) were excluded. An uncorrected height threshold of $p = .005$ and an extent threshold of 10 voxels were used.

Functional Connectivity

The functional connectivity was computed (separately for each participant) as a correlation between the average time course of signal intensity of all the activated voxels in each member of a pair of regions of interest (ROIs). A total of 21 functional ROIs were defined. Nine ROIs were defined bilaterally, which include inferior frontal gyrus (IFG), middle frontal gyrus (MFG), precentral gyrus (Precen), inferior parietal lobule (IPL), superior parietal lobule (SPL), fusiform gyrus (FG), cingulate gyrus (CINGG), insula, and inferior occipital gyrus (IOG). In addition to these 18 bilateral ROIs, 3 other ROIs were defined: the anterior cingulate gyrus (ACING), the supplementary motor area (SMA), and the right middle temporal gyrus (RMTG). A sphere was defined for each cluster (with a radius from 5 to 10 mm) that best captured the cluster of activation in the map for each group. The ROIs used in the analysis were each the union of the six spheres defined for the two groups in each of the three conditions. The activation time course extracted for each participant over the activated voxels within the ROI originated from the normalized and smoothed images, which were low-pass filtered and had the linear trend removed. The time course was extracted at a t threshold of 4.5, which corresponds to the individual participant's brain activation at a corrected p threshold of .05, thus making sure that the individual participants showed activation in each defined functional ROI. The defined ROIs had to show at least 12 voxels of activation to be considered for the functional connectivity correlation, i.e., the functional connectivity correlation is between active voxels in two given ROIs. The correlation was computed on the images belonging to all conditions, and it reflects the interaction between the activation in two areas while the participant is performing the task. Fisher's r to z′ transformation was applied to the correlation coefficients for each participant prior to averaging and statistical comparison of the two groups. Functional connectivity is simply the correlation of activation across regions and does not refer to anatomical connectivity.

Factor Analysis

A factor analysis of the functional connectivities was performed to indicate the groupings of the ROIs into networks based on the similarities of their time courses (Koshino *et al.* 2005). For each ROI pair, mean z'-transformed values of the functional connectivity measures were computed across participants for each group. The mean z'-transformed values were then converted back to correlation coefficients, and a correlation matrix was constructed for each group. The resulting connectivity matrices included 21 functional ROIs. An exploratory factor analysis (e.g., McLaughlin *et al.* 1992; Peterson *et al.* 1999) was then performed for each group separately. The logic behind the factor analyses was that each factor would correspond to a large-scale network of brain regions executing some high-level function (Mesulam 1990, 1998). Factor loadings represent the degree to which each of the ROIs correlates with each of the factors, and ROIs that had factor loadings of .5 or greater were taken into consideration in interpreting the results.

Results

Overview

The main finding was that the autism group showed a reduced level of brain activation in the simple inhibition condition relative to the control participants primarily in regions associated with inhibition (like middle or anterior cingulate cortex), and in the 1-back inhibition condition, a similar pattern occurred in these areas. In addition, the autism group showed more activation in bilateral premotor regions, areas associated with processing cues in task preparation. The participants with autism also showed reduced functional connectivity relative to the control participants between the anterior cingulate inhibition network and parietal regions during the working memory inhibition condition. At the behavioral level, there was no significant difference between the autism and control participants in performance.

Behavioral Results

There were no statistically reliable differences between the two groups in behavioral performance. Neither the reaction time (autism mean = 394 msec; control mean = 383 msec) nor the false alarm rate (autism mean = 17.2%; control mean = 19.6%) showed any reliable difference between the two groups. The autism group showed a greater effect of working memory load on false alarm rate. The autism group made more false alarm errors in the 1-back inhibition condition (21%) than in the simple inhibition condition (14%), whereas the control group showed no reliable difference between the two conditions in false alarm error rates (simple inhibition: 20%; 1-back inhibition: 19%), resulting in a reliable interaction between group and condition [$F(1,22) = 4.27$, $p < .05$]. Although the group by task interaction was expected, the pattern of results found here, with the autism group showing equivalent performance in the working memory condition, was not predicted.

Group Differences in Brain Activation

In the simple inhibition condition, the autism group showed reliably lower brain activation than control participants in several regions previously found to be involved in inhibition. These regions were right insula, right inferior frontal gyrus, right cingulate gyrus, and right premotor cortex (Figure 2 for reduced cingulate activation and Table 2 for the list of all activated regions). There seems to be two main networks involved in accomplishing response inhibition: 1) an inhibition network consisting of regions such as the cingulate cortex and insula, and 2) a strategic or executive network involving the prefrontal and parietal regions. The results showed lower activation in autism not only in the inhibition network but also in certain components of the executive network such as the right inferior frontal gyrus.

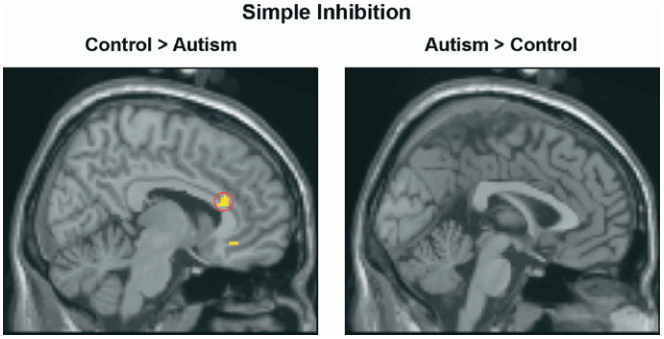

Figure 2. Group subtraction results in the simple inhibition condition. The control group showed greater cingulate activation than the autism group (left panel). The threshold for significant activation was $p < .005$ for a spatial extent of at least 10 voxels, uncorrected for multiple comparisons.

In the more demanding 1-back inhibition condition, the autism group again showed reliably lower brain activation in several regions, including the left anterior cingulate gyrus, left precuneus, and right angular gyrus (Figure 3 shows reduced cingulate activation and Table 3 has the list of all activated regions). On the other hand, the autism group showed more activation than control participants in left and right premotor regions. This condition is relatively difficult since it has both working memory and inhibition components. Unlike the simple inhibition condition, there was no group difference in right inferior frontal activation in 1-back inhibition. This may be because both groups were activating this region equally to keep up with the demands of working memory in this condition. The behavioral data showed that the autism group made reliably more errors in this condition compared with their performance in simple inhibition.

Unlike the simple inhibition and 1-back inhibition conditions, there was no group difference in activation in the cingulate cortex during the condition where no inhibition was involved. In other words, the cingulate activation difference between the groups emerged only when there was an inhibitory demand, with the autism group showing lower activation than control participants. This group (autism vs. control participants) × condition (inhibition vs. no inhibition) interaction was significant in the cingulate region [$t(22) = 5.43$, $p < .05$]. Cingulate cortex, especially the anterior cingulate, has been found to be involved in cognitive control processes, including several functions related to response inhibition such as error detection and conflict monitoring.

Factor Analysis

The main finding in the factor analysis was that in the autism group, unlike the control group, the inhibition network (consisting of anterior cingulate cortex, bilateral cingulate gyri, and bilateral insula) was grouped separately from other frontal-parietal areas (the right middle frontal, right inferior frontal, and right inferior parietal) in the 1-back inhibition condition. The inhibition network emerged as an isolated factor. This isolation of the inhibition network in autism is evident from the factor structure table (Figure 4), where the two red boxes indicate how the groups differed in this respect. This inhibition factor is Factor

Table 2. Group Differences in Activation for Control Participants and Participants with Autism During Simple Response Inhibition

Location of Peak Activation	Simple Inhibition			MNI Coordinates		
	Brodmann's Area	Cluster Size	*t*(22)	x	y	z
Areas in Which Control Participants Showed More Activation Than Participants with Autism						
Left Inferior Temporal Gyrus	37	82	4.56	−42	−46	−16
Right Parahippocampal Gyrus	27	120	4.48	26	−34	−8
Right Calcarine Sulcus	29, 30	260	4.39	16	−48	8
Right Premotor Cortex	6	74	4.32	24	0	60
Right Middle Cingulate Gyrus	31	58	4.17	14	−30	42
Right Postcentral Gyrus	40	114	4.09	40	−30	46
Left Postcentral Gyrus	40	35	4.08	−32	−44	56
Right Insula/Right Inferior Frontal Gyrus	13/47	50	3.94	40	14	10
Right Insula	13	20	3.28	38	14	−4
Left Lingual Gyrus	30	31	3.51	−12	−46	0
Areas in Which Participants with Autism Showed More Activation Than Control Participants						
None						

The threshold for significant activation was $p < .005$ for a spatial extent of at least 10 voxels, uncorrected for multiple comparisons. Region labels apply to the entire extent of the cluster. *t*-values, and MNI coordinates are for the peak activated voxel in each cluster only.

MNI, Montreal Neurological Institute.

2 (F2) for the autism group, which corresponds to Factor 1 (F1) for the control group. The autism group differed from the control participants in that their inhibition network seemed to be working by itself. In control participants, the areas of this network were grouped with right frontal and parietal areas, indicating a greater integration of the inhibition processes with the frontal-parietal processes.

Aside from the inhibition factor described above (one of the emerging factors for both groups), both groups had two additional factors that were identical. These factors were 1) the frontal-parietal (green boxes in Figure 4) with bilateral inferior frontal, precentral, inferior parietal, superior parietal, and supplementary motor areas grouped together (F1 for the autism group corresponding to F2 for control participants), and 2) the occipital-temporal (blue boxes in Figure 4) with left and right fusiform and left and right inferior occipital areas grouped together (Factor 3 [F3] for both groups).

Functional Connectivity

Based on the factor analysis results, a functional connectivity analysis grouped together those regions that belonged to a particular factor, essentially defining a network. This functional connectivity network analysis revealed that during the 1-back inhibition task, the autism group showed reliably reduced functional connectivity between the inhibition network and right inferior parietal areas, providing converging evidence to the factor analysis results [$t(22) = 2.65$, $p < .05$]. In addition, the inhibition network also showed lower functional connectivity with right inferior frontal gyrus in the autism group compared with control participants [$t(22) = 2.03$, $p < .05$]. In the simple inhibition condition, although the autism group showed the same pattern, the effect was not statistically reliable. In participants with autism, the inhibition network is not as well coordinated with the other networks and regions involved in performing the task.

Based on the prediction that the inhibition network would show underconnectivity with other regions for the autism group relative to the control participants, two planned contrasts comparing the group differences in connectivity between the inhibition network and right inferior frontal gyrus and right inferior parietal lobe were conducted. The results of this analysis of variance (ANOVA) confirmed that the inhibition network was functionally underconnected in the autism group with right inferior parietal lobe [$F(1,22) = 7.04$, $p < .05$] and with right inferior frontal gyrus [$F(1,22) = 4.13$, $p < .05$]. This functional connectivity difference was reliable only for the 1-back inhibition condition.

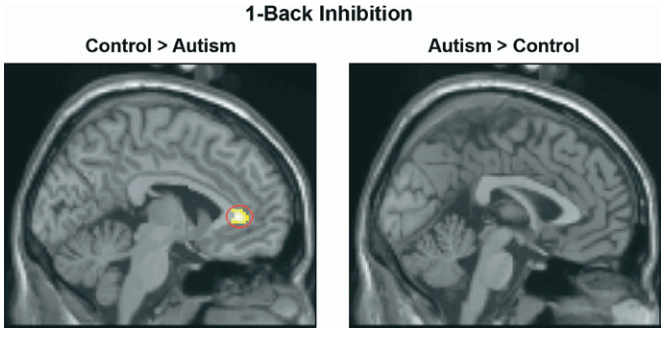

Figure 3. Group subtraction results in 1-back inhibition condition. The control group showed greater cingulate activation than the autism group (left panel). The threshold for significant activation was $p < .005$ for a spatial extent of at least 10 voxels, uncorrected for multiple comparisons.

Discussion

This study showed reliable group differences in brain activation in cortical regions involved in inhibitory control. In addition, these regions were found to be functionally underconnected with key frontal and parietal regions in participants with autism. The participants with autism showed reduced activation mainly in one region, the cingulate cortex. This hypoactivation in cingulate regions in autism is interesting considering the role of this region in inhibitory control and the functional and structural abnormalities found by previous studies in the cingulate regions in autism. The cingulate cortex has been found to play a central role in several functions associated with response inhibition,

Table 3. Group Differences in Activation for Control Participants and Participants with Autism During 1-Back Inhibition Task

Location of Peak Activation	N-Back Inhibition: Brodmann's Area	N-Back Inhibition: Cluster Size	N-Back Inhibition: *t*(22)	MNI Coordinates: x	MNI Coordinates: y	MNI Coordinates: z
Areas in Which Control Participants Showed More Activation Than Participants with Autism						
Left Anterior Cingulate Gyrus	24	115	4.73	−4	38	4
Left Middle Occipital Gyrus	19, 39	137	4.45	−40	−80	34
Left Calcarine	30	257	4.43	−16	−54	12
Right Calcarine	29	100	3.48	16	−50	10
Right Angular Gyrus	39	31	3.99	48	−72	32
Left Precuneus	7	41	3.46	−8	−64	32
Areas in Which Participants with Autism Showed More Activation Than Control Participants						
Left Premotor	6	26	4.29	−28	−4	66
Right Premotor	9	50	3.44	56	8	38

The threshold for significant activation was $p < .005$ for a spatial extent of at least 10 voxels, uncorrected for multiple comparisons. Region labels apply to the entire extent of the cluster. *t*-values and MNI coordinates are for the peak activated voxel in each cluster only.

MNI, Montreal Neurological Institute.

such as monitoring task performance, conflict monitoring, and error detection (Botvinick *et al.* 2004; Bush *et al.* 2000). All these functions are part of the type of complex information processing in which people with autism have difficulty (Minshew *et al.* 1997). According to Minshew *et al.* (2002), autism may reflect a disturbance in resolving conflict between different strategies and monitoring and switching strategies to achieve goals. Lower levels of cingulate activation in participants with autism might be the source of difficulty in these functions. Morphometric studies have found anterior cingulate in autism to be reliably smaller than the control participants (Haznedar *et al.* 1997, 2000). A diffusion tensor imaging study found reduced fractional anisotropy in anterior cingulate cortex in autism (Barnea-Goraly *et al.* 2004). The finding of hypoactivation in the cingulate region in the present study adds further evidence to the atypical functioning associated with this region in autism. But as we note below, the breadth of the activation abnormalities in autism makes it unlikely that any one region is the single source of the problem. We ultimately attribute the abnormal activation to interregional underconnectivity, particularly between frontal and other regions.

Another source of evidence of lower inhibitory control in autism is related to the reduced activation in the anterior insula. This may indicate not only the difficulties people with autism have in controlling attention but also in executive planning to accomplish the task. Insula is commonly activated in tasks that require executive control of attention, including those that require manipulation of information in working memory (Wager and Smith 2003), response inhibition, shifting attention (Wager *et al.* 2004), and suppression of conscious thoughts (Wyland *et al.* 2003). The insula is closely connected to the prefrontal cortex and anterior cingulate gyrus and forms part of a frontal-striatal attentional network (Schmitz *et al.* 2006). The hypoactivation in insular cortex along with cingulate cortex in autism suggests a disordering of inhibitory control in the task. In the only published neuroimaging study of response inhibition in autism, Schmitz *et al.* (2006) found increased activation in people with autism spectrum disorders in left inferior frontal areas during motor inhibition and in left insula during the Stroop task. The participants in that study were diagnosed with Asperger Syndrome (AS), unlike the high-functioning individuals with autism in our study. The increased activation in AS in their study may not be related to inhibition per se since the activation was in the left hemisphere. It may be possible that the AS participants (who have no language delay and are generally verbal) in that study tended to use internal verbalization during the inhibition task, hence the increased left inferior frontal gyrus activation. The increased insula activation in their study was again in the left hemisphere (for the Stroop task). Left insula also has been found to be active when participants do subvocal rehearsal (Paulesu *et al.* 1996).

Behaviorally, the participants with autism performed as well as the control participants in the simple inhibition condition; however, they made more errors in 1-back inhibition. In other words, when response inhibition had an additional working memory component, there was a decline in the performance of participants with autism. The addition of a working memory component may have undermined the effectiveness of any

	Autism				Control			
Factor	F1	F2	F3		F1	F2	F3	
Anterior cingulate gyrus	.	0.80	.		0.84	.	.	
L cingulate gyrus	.	0.73	.		0.68	.	.	
R cingulate gyrus	.	0.80	.		0.85	.	.	
L insula	.	0.54	.		0.56	.	.	
R insula	.	0.50	.		0.60	.	.	
Supplementary motor area	0.56	.	.		.	0.51	.	
L inferior frontal gyrus	0.65	.	.		.	0.60	.	
R inferior frontal gyrus	0.71	.	.		.	0.55	.	
L middle frontal gyrus	.	.	.		.	.	.	
R middle frontal gyrus	.	.	.		0.50	.	.	
L precentral gyrus	0.56	.	.		.	0.50	.	
R precentral gyrus	0.68	.	.		.	0.61	.	
L intraparietal sulcus	0.72	.	.		.	0.73	.	
R intlraparietal sulcus	0.73	.	.		0.52	0.58	.	
L superior parietal lobe	0.71	.	.		.	0.75	.	
R superior parietal lobe	0.68	.	.		.	0.70	.	
L fusiform gyrus	.	.	0.75		.	.	0.70	
R fusiform gyrus	.	.	0.65		.	.	0.70	
R middle temporal gyrus	.	.	.		.	.	.	
L inferior occipital gyrus	.	.	0.80		.	.	0.70	
R inferior occipital gyrus	.	.	0.68	Total	.	.	0.74	Total
Eigen value	4.82	3.58	2.95	11.35	4.61	4.45	2.94	12.00
% variance explained				**54.03**				**57.16**

F1: Frontal and parietal
F2: Inhibition
F3: Occipital and inferior temporal

F1: Inhibition, Right frontal & parietal
F2: Frontal and parietal
F3: Occipital and inferior temporal

Figure 4. Factor analysis.

coping strategy that people with autism may have used in the simple inhibition condition.

Functional Connectivity

Although the anterior cingulate cortex (ACC) plays an important role in inhibitory control, there may be other cortical regions working in synchrony with ACC in accomplishing inhibitory control. The results from factor analysis and functional connectivity analysis in the present study showed a reliably lower degree of synchronization and coordination between key cortical networks in autism compared with the control group. Weaker integration was found in the connections between the ACC inhibition system (consisting of regions such as anterior cingulate gyrus, middle cingulate gyrus, and insula) and the right frontal-parietal inhibition system (right inferior frontal, middle frontal, and right inferior parietal regions). While the ACC system was functioning out of synchrony with other networks in the autism group, this system was synchronized with right frontal and parietal regions in the control participants. According to Garavan *et al.* (2002), the ACC system is involved in relatively faster and urgent inhibition, whereas the frontal-parietal system is involved in more deliberate and controlled inhibition. In control participants, these two inhibition systems seem to work together as an integrated system recruiting more attentional resources. The inferior parietal regions, in conjunction with activation in ACC, have been related to error detection (Carter *et al.* 1998), response conflict (Braver *et al.* 2001; van Veen *et al.* 2001), and to visual-spatial alerting and orienting (Corbetta *et al.* 2000; Coull *et al.* 1996). All these functions are part of constructing and executing metacognitive strategies and having inhibitory control.

While several studies have explored the role of prefrontal cortex in cognitive control (Miller and Cohen 2001 has a review), the functional connectivity between cognitive control in prefrontal cortex and other brain regions has not been addressed. Orbitofrontal and anterior cingulate cortex have bilateral cortical connections within ventral and dorsal prefrontal cortex, insula, and parietal cortex, as well as with subcortical connections with amygdala, striatum, and thalamus (Cavada *et al.* 2000; Musil and Olson 1988; Vogt and Pandya 1987). Egner and Hirsch (2005) recently explored the functional integration in cognitive control and found that the activation in prefrontal regions was accompanied by increased functional integration with right temporal and parietal areas. The lower functional connectivity between the ACC system and right hemisphere frontal and parietal regions in autism in our study provides an important insight into the difference in inhibitory control between the two groups in this task. It should be noted here that the activation and connectivity differences are occurring despite no behavioral difference between the groups. That gives further evidence to the fact that the differences between the two groups are at a finer level, with the autism group accomplishing the task always through a different route. Some studies have reported that people with autism have abnormalities in prefrontal and anterior cingulate cortex metabolism (Carper and Courchesne 2005; Horwitz *et al.* 1988; Siegel *et al.* 1995) and anatomical abnormalities in regions involved in inhibition (Schmitz *et al.* 2006). Allman *et al.* (2001) suggested that the spindle cell structures of the anterior cingulate may serve to connect widespread areas of the brain to achieve the synchronization of information in difficult problem-solving situations. Structural and functional abnormalities in the cingulate cortex in autism could be symptomatic of a lower level of connectivity in autism.

It should be noted here that the reduced functional connectivity in autism does not result from reduced activation. First and most importantly, in the vast majority of the ROI pairs in which underconnectivity was observed in autism, there was no reduction of activation in autism. Second, in the case where there was lower activation in the autism group (involving anterior cingulate cortex), the underconnectivity was found between a network (set of ROI pairs), which included several other areas such as middle cingulate, insula, and right parietal region. In these other areas, there was no activation difference between the groups, and still these ROIs showed lower functional connectivity with the right parietal region in the autism group. Third, other studies have found underconnectivity in several individual ROI pairs where there was no reduction in activation, such as a study on executive functioning which found, despite having an equal amount of activation in autism and control groups, that there was widespread functional underconnectivity in the autism group (Just et al, in press). The findings strongly indicate that underconnectivity does not stem from a reduction in activation.

Successfully withholding a response to the "no-go" trials is argued to represent inhibitory control over a prepotent response, typically resulting in activation of prefrontal, parietal (predominantly right hemisphere), and midline (ACC and pre-SMA) regions (Garavan *et al.* 2002; Liddle *et al.* 2001; Rubia *et al.* 2003; Watanabe *et al.* 2002). These regions interact, coordinate, and function as a unit to accomplish inhibition. Because of the cortical underconnectivity in autism, the interregional coordination may be particularly stressed in complex tasks, such as 1-back inhibition in the present study, that involve creating a novel strategy, flexibility, and monitoring performance. A novel task requires the underpinning brain regions to dynamically configure themselves into an appropriate network, and the poorer connectivity in autism impairs this dynamic ability. The compensatory strategy that often arises in autism under such circumstances is a reversion to relying on lower level perceptually based strategies that require less connectivity to frontal areas.

Reduced functional connectivity in people with autism has been found in diverse tasks, such as sentence comprehension (Just *et al.* 2004) and verbal working memory (Koshino *et al.* 2005). Findings from these studies provide evidence for the generality of the underconnectivity across tasks, as well as the specificity of the underconnectivity to frontal cortical regions. The larger connectivity differences were found mainly in the long-distance connections between frontal and other regions. Recently, we found frontal-parietal underconnectivity in an executive function task (Just et al, in press) and in a language comprehension task involving visual-spatial imagery (Kana *et al.* 2006). This is consistent with other studies that found reduced long-distance structural (Courchesne and Pierce 2005) and functional (Castelli *et al.* 2002) connectivity.

In conclusion, the findings of this study suggest that in individuals with autism, inhibitory processes do not function as part of a coordinated and synchronized cortical network. Future neuroimaging studies of autism may further modify this account, explaining the breadth and the specificity of the atypical inhibitory function in autism.

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