



Individuals with schizophrenia present hypo- and hyperactivation during implicit cueing in an inhibitory task

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Background: The primary purpose of this investigation was to assess the neural correlates of implicit cueing during an inhibitory task in schizophrenia when performance accuracy was matched with healthy comparison subjects.

Methods: We compared 17 individuals with chronic schizophrenia (SZ; medicated, 13.9 average years of illness) and 17 healthy comparison subjects (HC) matched for hit and false alarm rates, age, and education on a visual Go/Nogo task during functional magnetic resonance imaging. In this task, one of the go stimuli also served implicitly as a cue predictive of a subsequent inhibitory (Nogo) trial.

Conclusions: Findings suggest that even when matched for overall performance accuracy, individuals with SZ exhibit difficulties with inhibition and cue processing that may relate to core deficits in cognitive control and stimulus processing. In particular, these findings point towards an important role of the parietal cortex for cued inhibitory processes in healthy populations.

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Keywords: Schizophrenia; fMRI; Inhibition; Predicting cues; Parietal cortex; Prefrontal cortex; Insula

Introduction

Inhibition is the process by which the execution of a thought, action, or emotion is overridden or reversed. Whether it involves stopping at a red light or not spending beyond one's means, inhibition is an important function for daily life. Several fMRI studies with healthy volunteers have identified critical neural substrates of inhibition during Go/Nogo performance, which

include the inferior and middle frontal cortices (Garavan et al., 2003, 1999; Mathalon et al., 2003; Maguire et al., 2003; Mostofsky et al., 2003; Menon et al., 2001; Liddle et al., 2001; Konishi et al., 1999), inferior parietal lobe (Garavan et al., 2003, 2002; Mathalon et al., 2003; Maguire et al., 2003; Liddle et al., 2001; Rubia et al., 2001), anterior cingulate (Botvinick et al., 1999; Rushworth et al., 2005), precuneus (Mathalon et al., 2003; Maguire et al., 2003; Liddle et al., 2001; Rubia et al., 2001), insula (Mathalon et al., 2003; Garavan et al., 2002, 1999; Kawashima et al., 1996), and superior temporal gyrus (Mathalon et al., 2003; Liddle et al., 2001).

In some situations, inhibition needs to occur suddenly, without any predicting cues. In others, however, the need to withhold an action may be signaled by an external stimulus, which may help to facilitate inhibition. For example, a driver approaching a green traffic light (go stimulus) that turns into a yellow light (predictive cue) is warned that an inhibitory action may be required (the upcoming red light presumably serves as a Nogo stimulus). Thus, the yellow light is a cue that signals the impending inhibition of an ongoing action. The study of these types of cues that signal an upcoming change in behavior is of crucial importance because it helps one to understand how the brain computes inhibiting actions.

Failure of inhibitory control, e.g., using the prepulse inhibition paradigm, has been proposed as one of the key endophenotypes of schizophrenia (SZ) (Cadenhead et al., 2002). Individuals with SZ have difficulty overcoming prepotent response tendencies (Ford et al., 2004), and some inhibitory paradigms using explicit predictive cues have demonstrated longer reaction times (RTs) and more errors in SZ subjects than in healthy comparison subjects (HC) (Fallgatter et al., 2003; Fallgatter and Muller, 2001; Fallgatter, 2001; Javitt et al., 2000). Other studies have found that SZ subjects present impaired cue recognition in a social context (Corrigan and Nelson, 1998; Ito et al., 1998; Hall et al., 2004), particularly in those with positive symptoms (Hall et al., 2004; Crider, 1997). Considering the above, we suggest that one of the possible contributors to inhibitory failure in SZ may relate to inefficient

Abbreviations: PANSS, Positive And Negative Symptom Scale; BPRS, Brief Psychiatric Rating Scale; NART, National Adult Reading Test; CWIT, Color-Word Interference Test.

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context processing. Furthermore, endogenous stimulation (i.e., positive symptoms) is likely to interfere with contextual (exogenous) information announcing an upcoming inhibition. Nevertheless, no study to date has explored the behavioral and neural effects of implicit cueing and its relation to positive symptomatology in SZ using a simple inhibition task and fMRI.

The Go/Nogo variant in this study incorporates cues predictive of the need to inhibit responses. Detection of visual predictive cues has been associated with inferior parietal lobe function (e.g., Mesulam, 1999; Stoet and Snyder, 2004). Assuming that individuals better able to process these cues will benefit from faster performance, and with the purpose of studying how SZ individuals benefit from these cues, we selected those with correct (i.e., hit) and erroneous (i.e., false alarm) rates matched to HC participants. We expect that compensated performance in SZ will require greater cognitive effort associated with cue processing. Given the importance of the parietal cortices in visual context and inhibition processing, we hypothesized that the posterior parietal cortex would differentially activate during cue processing. Moreover, if equal performance among both groups is achieved via more effortful processing, we expect an increased activation in this area in SZ relative to HC subjects. Furthermore, considering previously reported context processing deficits during inhibition in relation to positive symptoms (Servan-Schreiber et al., 1996), we predict that those with higher levels of positive symptomatology will require heightened parietal effort to achieve healthy performance.

Methods and materials

Subjects

Thirty-two SZ and 30 HC subjects participated in the study, performing the Go/Nogo task during fMRI. After matching for age, education, and performance accuracy (i.e., hit and false alarm rates), 17 individuals from each group were retained and used for further analyses. SZ individuals were recruited using infrastructure created by the Mental Illness, Research, Education, and Clinical Center (MIRECC) at the San Diego VA Medical Center. SZ subjects were also recruited from University of California San Diego (UCSD) Psychiatric Outpatient Services (a large outpatient facility with over 2500 patients enrolled), Board and Care facilities in San Diego County, and San Diego County Outpatient Clinics. Individuals were diagnosed using the Structured Clinical Interview for DSM-IV (SCID; Spitzer et al., 1992) by a psychiatrist, psychologist, or trained research assistant. Comparison subjects were recruited by newspaper advertisement and word-of-mouth, screened by telephone using questions from the SCID, and excluded for any significant Axis I psychiatric illness. Prospective SZ and HC participants were excluded if they met DSM-IV criteria for alcohol or drug abuse within 30 days prior to the study. In addition, subjects were excluded for significant head injury and neurological or other medical conditions compromising the central nervous system. SZ subjects were taking stable doses of antipsychotic medications (assessed through self-report and medical records). The study was approved by the UCSD Human Research Protection Program. Each subject gave written informed consent and completed a post-consent questionnaire to demonstrate the capacity to provide informed consent.

Materials

Demographics and personality/symptom assessment

Subjects reported their age, gender, race/ethnicity, handedness, and years of education (see Table 1). SZ symptoms were assessed using the 18-item Brief Psychiatric Rating Scale (BPRS; Faustman and Overall, 1999) and the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). All subjects completed the National Adult Reading Test (NART; Nelson, 1991). Sixteen subjects from each group completed the D-KEFS Color–Word Interference Test CWIT; (Delis et al., 2001).

Go/Nogo task

Participants view a serial presentation of blue shapes on a computer screen, all according to the same fixed stimulus sequence: 18 blocks of 10 trials each with baseline rest periods of 0–40 s each between blocks. The stimuli consist of large circles ($n = 64$), small circles ($n = 16$), large squares ($n = 43$), and small squares ($n = 57$). Each stimulus appears for 200 ms. Subjects are instructed to press a button each time a large circle, small circle, or large square appears (go), and not to press the button when a small square is shown (Nogo). The intertrial interval is 1500 ms.

Unbeknownst to subjects, the large square serves not only as an explicit go stimulus, but also implicitly as a predictive cue in that it is frequently followed by a Nogo trial. The cues appear in 24% of the trials, and these (i.e., the cues) are followed by a small square 86% of the time.

Statistical analysis

Behavioral data

Demographic and neuropsychological assessment comparisons were made by unpaired t test. To assess behavioral task measures, four unpaired t tests were run, using each of the following dependent measures: hit rate, false alarm rate, beta (bias toward making versus withholding a response) and d' (perceptual discrimination of go versus Nogo stimuli). Because there are never two Nogo stimuli in a row in the task, Nogos serve as perfect predictors of upcoming go stimuli and may speed responses to them. To assess this, a $2 \times 2 \times 2$ repeated measures ANOVA was performed with RT as the dependent measure. Group (SZ versus HC) was the between-groups factor while Previous Trial (go versus Nogo) and Go Type (large square versus large circle) were the within-subjects factors. Finally, to assess whether cueing had an impact on subsequent trial response times, RT was compared on go trials following cues versus noncues using a 2×2 repeated measures ANOVA. Group was the between-groups factor while Previous Trial (large square versus large circle) was the within-subjects factor. Small circles were excluded from these last two analyses, in the first case because they never follow Nogo stimuli, providing no comparison with RTs following go stimuli, and in the second case because relative to large squares, small circles are very infrequent, whereas large circles have a more comparable frequency.

fMRI protocol and image analysis pathway

All data were preprocessed, normalized to Talairach coordinates (Talairach and Tournoux, 1988) and analyzed with the AFNI software package (Cox, 1996). For preprocessing, voxel time series data were interpolated to correct for nonsimultaneous slice acquisition within each volume and corrected for three-dimension-

Table 1

Demographic, neuropsychological, and diagnostic characteristics of individuals with schizophrenia and healthy comparison subjects participating in an fMRI study of Go/Nogo with predicting cues

Variable	Schizophrenia subjects			Comparison subjects			<i>P</i>
	Mean	SD	Range	Mean	SD	Range	
Age (years)	40.88	7.52	27–51	39.82	7.99	26–56	0.69
Education	13.44	1.25	12–16	13.65	1.37	10–16	0.65
NART errors	28.65	13.79	7–50	23.12	12.48	9–57	0.22
CWIT color naming C1	7.25	3.34	1–12	9.25	2.59	4–13	0.07
CWIT word reading C2	6.93	3.47	1–14	9.31	4.03	1–15	0.09
CWIT inhibition C3	6.69	3.61	1–13	9.94	3.55	1–17	0.01
CWIT inhibition/switching C4	6.94	3.73	1–12	10.50	3.92	1–19	0.01
Age of onset (years)	26.82	6.45	18–38				
Duration of illness (years)	13.91	9.45	0.5–30				
PANSS positive	17.75	21.81	6–97				
PANSS negative	17.07	10.07	0–32				
PANSS general	26.40	12.42	7–48				
BPRS total	37.18	12.87	24–67				
	<i>N</i>		%	<i>N</i>		%	<i>P</i>
Right handedness	14		82	16		91	0.60
Caucasian ethnicity	11		64	9		52	0.48
Male gender	13		76	14		82	0.67
Hospitalization outpatient status	17		100				
Schizophrenia subtype							
Paranoid	12		71				
Undifferentiated	4		23				
Residual	1		6				
Antipsychotic medication							
Atypical ^a	14		82				
Typical ^b	1		6				
Both ^{a,b}	2		12				

^a Quetiapine, Risperidone, Olanzapine, Clozaril

^b Thioridazine, Haloperidol

al motion. Motion-corrected voxel time series data were visually inspected to remove large movement artifacts. Preprocessed time series data for each subject were analyzed using a multiple regression model consisting of ten regressors. Three regressors were used to model residual motion (in the roll, pitch, and yaw directions). Two regressors – a baseline and a linear trend – were used to eliminate slow signal drifts. There were five orthogonal regressors of interest: (1) Large Square (Go/Cue), (2) Large Circle (Go/Noncue), (3) Small Circle (Go/Noncue), (4) Small Square when preceded by a Large Square (Cued-Nogo), and (5) Small Square when preceded by a Small Circle or Large Circle (Uncued-Nogo). These five regressors were created based on the sequence of stimulus events as described above and convolved with a model of a prototypical hemodynamic response prior to inclusion in the regression model.

The AFNI program 3dDeconvolve was used to calculate the estimated voxel-wise impulse response function for each regressor and to generate three contrasts: (1) Inhibition (Nogo–Go), (2) Cue Processing (Go/Cue–Go/Noncue), and (3) Cued Inhibition (Cued-Nogo–Uncued-Nogo). The first contrast, used to compare go and Nogo activation collapsing across cue conditions, measures inhibition and was created for comparison with previous Go/Nogo studies. The other two contrasts were created to examine the effect of predictive cues. Thus, the second contrast compared the go stimulus that served as a cue (Large Square) against go stimuli that did not (Large Circle, Small Circle), and the third contrast was created to examine the impact of cueing on Nogo-related

activation. A Gaussian filter with FWHM 6.0 mm was applied to the voxel-wise percent signal change data to account for individual variations of anatomical landmarks. Voxel-wise *t* tests were used to identify the brain areas in which the percent signal change associated with each contrast was significantly different between groups. A threshold adjustment method based on Monte Carlo simulations was used to guard against identifying false positive areas of activation (Forman et al., 1995). Based on these simulations, it was determined that a voxel-wise a priori probability of 0.05 would result in a corrected cluster-wise activation probability of 0.05 when a minimum cluster volume of 1024 μ l and a connectivity radius of 4.0 mm was considered. All clusters surviving these thresholds were reported in Tables 3 and 4. The listed cortical areas are based on Talairach and Tournoux (1988) atlas in AFNI. The average BOLD signal within each cluster of activation was extracted for each subject. These were later correlated with behavioral and symptom measures. A group average of the BOLD signal was then calculated for each condition.

Procedure

After consenting, participants completed interviews and neuropsychological tests. During a second visit, they were given task instructions and completed a practice Go/Nogo run immediately prior to the fMRI session to familiarize them with the task and control for confounding effects of learning from a task-naïve state

during the scan session. Subjects performed the task during the fMRI session using button press responses. Afterwards, all subjects completed a post-task questionnaire to gauge their understanding of it. Before leaving, subjects were debriefed and paid for participating.

Results

Task performance

As reflected on Table 2, there were no group effects on measures of performance accuracy (i.e., false alarm and hit rate) or beta. HC participants had higher d' scores, suggesting they were better able to differentiate go and Nogo stimuli than SZ subjects. d' analysis was re-run after one SZ subject was eliminated due to a substantially low d' score (i.e., 2.73 standard deviations below the SZ group mean). The difference between groups was reduced but still marginally significant ($t = 1.97$, $P = 0.058$). RT was significantly longer on trials following a go trial than a Nogo trial ($F = 109.27$, $df = 1, 32$, $P = 0.00$) and significantly longer for the SZ than the HC group ($F = 4.86$, $df = 1, 32$, $P = 0.03$). There were no significant RT interactions in this analysis. When comparing go trials following large squares (cues) versus large circles (noncues), RT was faster following cues ($F = 8.22$, $df = 1, 32$, $P < 0.01$). A group interaction ($F = 5.30$, $df = 1, 32$, $P = 0.03$) and follow-up t tests revealed that this was due entirely to a difference among the HC subjects ($P < 0.01$). There was no difference within the SZ group ($P > 0.6$).

Imaging data

Task effect

The first contrast (Nogo–Go) was computed to reveal regions activated during inhibition. Several areas survived thresholding but all showed greater activation during Go than Nogo trials. These included the bilateral anterior cingulate, bilateral medial frontal gyrus, bilateral paracentral lobule, left superior parietal lobule, and left precuneus.

Areas activated in cue processing (Go/Cue–Go/Noncue) included the bilateral inferior and right middle frontal gyri, right inferior parietal lobule, bilateral anterior cingulate, bilateral thalamus, and bilateral caudate.

Regions that survived thresholding after the cued inhibition (Cued-Nogo–Uncued-Nogo) included the left insula and left precuneus. This contrast revealed activation related to the effect of cueing on inhibition trials.

Group comparisons

In the inhibition (Nogo–Go) contrast, HC showed greater activation than SZ subjects in areas including the bilateral anterior cingulate and left middle frontal gyrus (see Table 3 and Fig. 1). Activation in this latter area was positively correlated ($P = 0.03$, $r^2 = 0.15$) with C3 Inhibition (Delis et al., 2001) (all subjects) but not with C4 Inhibition-Switching Scaled Score of CWIT ($P = 0.09$, $r^2 = 0.1$).

The SZ group activated the following areas with greater intensity in the cue processing (Go/Cue–Go/Noncue) contrast: bilateral anterior cingulate, bilateral inferior frontal gyrus (see Fig. 2), left insula, left inferior temporal gyrus, right paracentral lobule, and left parahippocampal gyrus (see Table 4).

Finally, during cued inhibition (Cued-Nogo–Uncued-Nogo) the SZ group had greater activation in the left precuneus (see Fig. 2) and left superior temporal gyrus than the HC group (see Table 4). Moreover, among SZ individuals, activation in the former area was significantly correlated with PANSS general score ($P = 0.048$, $r^2 = 0.27$), although not with BPRS total score. Follow-up tests revealed a marginally significant correlation with PANSS positive ($P = 0.055$, $r^2 = 0.26$) but not PANSS negative.

Correlations of task performance and cue processing

Due to marginal differences in d' , post hoc analysis was performed to investigate how difficulty differentiating go and Nogo stimuli related to brain behavior during cue processing in 16 SZ individuals. We selected several regions of interests defined by the Talairach Daemon atlas (Lancaster et al., 2000), including the bilateral medial prefrontal cortex, insula and amygdala. The first of these a priori areas was selected due to its role in cognitive control and conflict monitoring (Ridderinkhof et al., 2004). Furthermore, in a previous imaging study that assessed the neural correlates of anticipation (Simmons et al., 2004), we observed the anticipatory role of the insula, which is known to have afferent and efferent connections to the medial prefrontal cortex and several nuclei of the amygdala (Augustine, 1996). Based on these areas of interests, it was determined via simulations that a voxel-wise a-priori probability of 0.05 would result in a corrected cluster-wise activation probability of 0.05 if a minimum volume of 256 μ l and 4 connected voxels. This resulted in significant activation clusters in the insula ($P = 0.001$, $r^2 = 0.54$) and dorsal anterior cingulate cortex (dACC; $P = 0.023$, $r^2 = 0.32$) (see Fig. 3).

Post-task questionnaires

Post-task questionnaire responses suggest that both groups were equally engaged in the task. No differences were found between

Table 2
Go/Nogo task measures of performance accuracy, response bias, and perceptual sensitivity

Measures	Schizophrenia subjects ($n = 17$)		Comparison subjects ($n = 17$)		t	P
	Mean	SD	Mean	SD		
Performance accuracy						
Hit rate	0.966	0.050	0.983	0.030	1.18	0.24
False alarm rate	0.143	0.080	0.094	0.093	−1.65	0.10
Response bias						
Beta	0.588	1.027	0.416	0.419	−0.63	0.52
Perceptual sensitivity						
d'	3.171	0.555	3.654	0.680	2.26	0.03

t Scores refer to differences between Schizophrenia and Comparison subjects.

Table 3

Regions of different significant activation between 17 Individuals with schizophrenia (SZ) and 17 healthy comparison (HC) subjects

Cortical areas (within cluster)	BA	L/R	Coordinates (center of cluster) ^a			Cluster volume (μ l)	<i>t</i> value	Figure
			<i>x</i>	<i>y</i>	<i>z</i>			
Anterior cingulate	32	L/R	2	38	−2	3648	3.79	
Cingulate gyrus	31	R	16	−26	34	1472	3.59	
Dorsal anterior cingulate	24	L/R	−7	−1	35	1344	4.97	1.A
Middle frontal gyrus	9	L	−27	33	26	1024	3.80	1.B

^a All coordinates are Talairach coordinates (*x*, *y*, *z*). Cortical areas are based on Talairach Daemon software (Lancaster et al., 2000).

groups in items of motivation (scale 1–5; HC: 4.190.98; SZ: 4.18 \pm 0.95; $P > 0.9$), interest (scale 1–4; HC: 3.50 \pm 0.89; SZ: 3.24 \pm 1.09; $P > 0.4$), or attention (scale 1–4; HC: 3.75 \pm 0.58; SZ: 3.53 \pm 0.72; $P > 0.3$). Responses to the item “Do you think the blue shapes were presented in a sequential pattern; if so, can you describe it?” provided no evidence that SZ or HC participants were aware of any pattern sequence. To the item “What thoughts did you have during the task?” one of the 34 participants (HC) responded that “[he] could try to anticipate the next shape by trying to figure out the pattern.”

Discussion

This study compared how individuals with SZ process predictive cues in order to aid inhibition. To do so, one of the go stimulus types in a Go/Nogo task also served implicitly as a relatively reliable signal that the next trial would present a Nogo. There were three main findings: the SZ (versus the HC) group presented: (1) diminished dACC and dorsolateral prefrontal cortex (DLPFC) activation during inhibition (i.e., Nogo trials versus go trials), (2) increased inferior frontal gyrus activation during implicit cue trials (i.e., cue/go trials as

contrasted with noncue/go trials), and (3) heightened left precuneus activation during inhibitory trials following implicit cueing (i.e., Nogo trials following cue/go trials as contrasted with those following noncue/go trials). Furthermore, task effect results revealed the involvement of the parietal cortex in cued inhibitory processing.

During inhibition processing, SZ individuals showed less task-related activation than HC individuals, notably in the left DLPFC and bilateral dACC. Regarding the former, a number of investigators have suggested that one of the most common neural dysfunctions in SZ is DLPFC hypoactivation (e.g., MacDonald and Carter, 2003a; Perlstein et al., 2003). Others have suggested that hypofrontality might be confounded by group performance differences (e.g., Ramsey et al., 2002) or that it only becomes evident when performance fails (Frith et al., 1995). MacDonald et al. (2005), however, found hypofrontality in first-episode SZ during trials with accurate performance, and present findings demonstrate hypofrontality in chronic SZ individuals matched with HC participants for overall high performance accuracy (i.e., low error rates). While our SZ individuals were not matched for d' , DLPFC hypoactivation has also been observed without d' differences (MacDonald and Carter, 2003b). Regarding the dACC, previous imaging studies have highlighted the importance

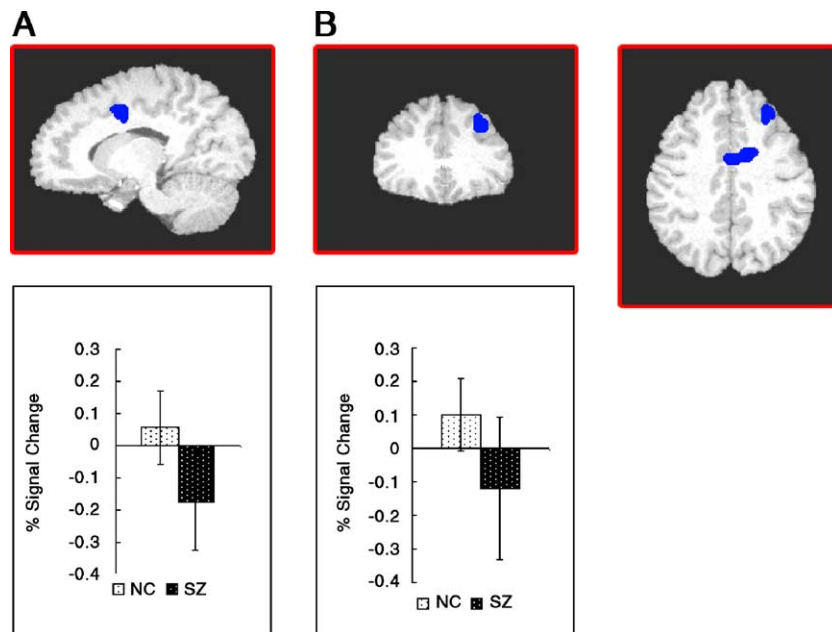


Fig. 1. Bilateral dorsal anterior cingulate (A) and left middle frontal gyrus (B) activation during Nogo-Go in subjects with schizophrenia (SZ) versus healthy comparison (HC) subjects (blue indicates less activation in SZ than HC). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

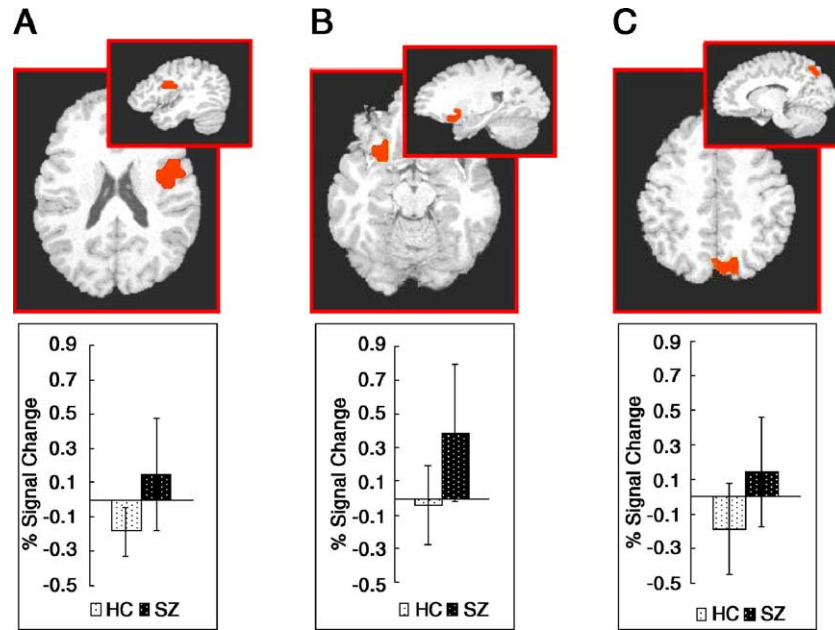


Fig. 2. Left inferior frontal (A) and right inferior frontal (B) activation during Go/Cue-Go? Noncue and left precuneus activation during Cued-Nogo (C) in subjects with schizophrenia (SZ) versus healthy comparison subjects (HC) (red indicates more activation in SZ than HC). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of this region during conflict monitoring and error detection (Carter et al., 1998), and a recently published study has demonstrated its role in the prediction of error-likelihood (Brown and Braver, 2005). This intriguing predictive attribute of the dACC was assessed in the context of announcing cues, thus, permitting an interpretative context for our results. Considering our findings in the frame of the Brown and Braver model, we can interpret the attenuated dACC activation during inhibitory trials as a failure to predict the likelihood of an error in the SZ group. Because performance levels were equally adequate in both groups, we may suggest that the SZ group compensated for this lack of error-likelihood prediction through parietal hyperactivation when processing the predictive stimulus (i.e., cues). Moreover, individuals with SZ have shown diminished activity in this area along with

poorer performance adjustment after error commission (Carter et al., 2001). Furthermore, during inhibition, SZ individuals have difficulty developing a prepotent response bias (Ford et al., 2004), as opposed to healthy individuals who are able to establish a response pattern (i.e., predisposition to press or “go”) that is overridden when a change is perceived (i.e., Nogo stimulus). SZ individuals, but not HC, seem to evaluate each stimulus on a trial-by-trial basis, making a deliberate choice and experiencing the same amount of conflict during both action and inhibition. Taken together, our findings replicate those of DLPFC dysfunction in SZ (Perlstein et al., 2003; MacDonald et al., 2005) and provide further support for dACC hypoactivity found in this population due to (1) poor conflict monitoring (Laurens et al., 2003; Carter et al., 2001), (2) unsuccessful development of prepotent response bias (Ford et

Table 4

Regions of different significant activation between 17 Individuals with schizophrenia (SZ) and 17 Healthy comparison (HC) subjects

SZ > HCS: Go_{Cue} > Go_{Noncue}

Cortical areas (within cluster)	BA	L/R	Coordinates (center of cluster) ^a			Cluster volume (μ l)	<i>t</i> value	Figure
			<i>x</i>	<i>y</i>	<i>z</i>			
Inferior temporal gyrus	37	L	-44	-69	-1	2304	4.19	
Anterior cingulate	24	L/R	4	33	-1	1664	4.4	
Inferior frontal gyrus	47	R	25	15	-11	1536	3.73	2.B
Inferior frontal gyrus, insula	13	L	-41	0	21	1472	3.76	2.A
Insula	13	L	-36	-37	18	1280	3.53	
Paracentral lobule	5	R	3	-40	60	1088	4.38	
Parahippocampal gyrus	19	L	-29	-46	-3	1024	4.15	

SZ > HCS: Nogo_{Cued} > Nogo_{Uncued}

Cortical areas (within cluster)	BA	L/R	Coordinates (center of cluster) ^a			Cluster volume (μ l)	<i>t</i> value	Figure
			<i>x</i>	<i>y</i>	<i>z</i>			
Superior temporal gyrus	22	L	-59	-22	4	1792	4.43	
Precuneus	7	L	-8	-71	43	1088	3.30	2.C

^a All coordinates are Talairach coordinates (*x*, *y*, *z*). Cortical areas are based on Talairach Daemon software (Lancaster et al., 2000).

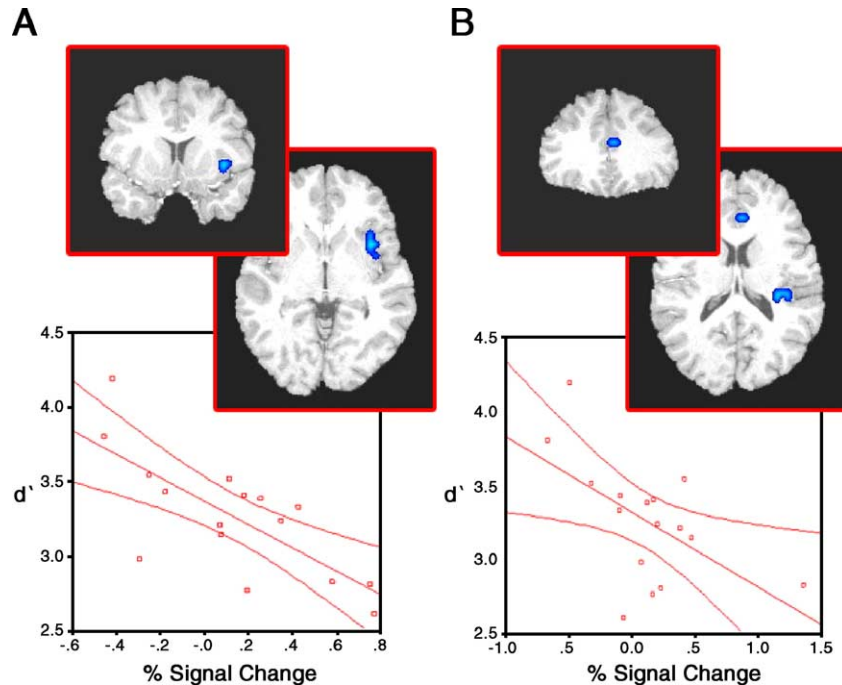


Fig. 3. Significant activation clusters related to d' scores in the insula (A) and dorsal anterior cingulate cortex (B) of individuals with schizophrenia during cue processing.

al., 2004) as well as provide (3) preliminary findings for a deficient prediction of error-likelihood in the dACC of SZ individuals.

Neuroimaging studies with healthy volunteers (Schmid et al., 2001; Adam et al., 2003) have demonstrated the importance of the parietal cortex in processing relevant predictive information. One of the objectives of this study was to evaluate the importance of this region during the processing of predictive inhibitory cues in the general population. Results from several studies highlight the importance of this structure in visuospatial attention (Stoet and Snyder, 2004; Astafiev et al., 2003), linking temporally contiguous events (Maguire et al., 1999), and planning for movement execution (Bunge et al., 2002; Astafiev et al., 2003). Moreover, cells in the parietal cortex of human (Toni et al., 2001) and nonhuman primates (Kalaska and Crammond, 1995) have been found active in response to cues to withhold or make a response. Our results confirm the role of the parietal cortex during cue processing and emphasize its importance in inhibitory situations. Focusing on between group differences during cue processing, our SZ group showed abnormally higher activation in the inferior frontal gyrus, a region commonly associated with inhibitory processes (e.g., Rubia et al., 2003; Aron et al., 2004) along with the perigenual anterior cingulate and insula. Considering the lack of group performance accuracy differences and the previously shown relationship between executive control demands (during a Go/Nogo task) and frontal activity (Bellgrove et al., 2004), this hyperactivation may reflect extra effort needed to perform on par with HC group.

In a recent study with healthy volunteers, Hester et al. (2004) described the brain correlates of a Go/Nogo task with predictive cues. Their results suggested that the precuneus, cingulate gyrus, middle temporal gyrus, and insula were reactive to cued inhibition (Nogo/cued–Nogo/uncued). In general, we found that the left precuneus activated differentially during predicted versus non-predicted inhibitory trials, which is consistent with the role of the

posterior parietal cortex in selective attentional processing, particularly in the visual domain (Baranov-Krylov and Shuvaev, 2005). Considering the involvement of the precuneus in the context of inhibition, both during cued inhibition (Hester et al., 2004) as well as during cue processing (present findings), this area may be crucial in the process of preparing the individual to engage the inhibitory circuitry. Furthermore, our results show that the SZ group presented greater activation than the HC group in this area during cue processing. A potential explanation might be that cued stimuli are complex (and potentially contradictory), as they contain information for both the current and following response, thus requiring greater cognitive effort for both groups but especially for the SZ. Similar to our analogy of the traffic light above, in which the yellow light is associated with conflicting information (i.e., it represents both a current go response but also signals upcoming inhibition), it appears that the precuneus, in a sensory level, processes the predictive component of the cued inhibition. On the other hand, in the context of executive functioning, the need for greater executive control in SZ individuals matches the finding of increased activation in the insula and anterior cingulate in relation to increased difficulty discerning go and Nogo stimuli (d'). Between group differences in the parietal lobe (sensory level), and within group differences in the insula and dACC (executive control level) might be explained by deficits in top-down modulation of cue processing due to the complex nature of the stimulus, which is consistent with previous findings of difficulty decoding nonverbal cues in SZ (Toomey et al., 2002) and complex stimuli in general (Carter and Neufeld, 1999). Furthermore, the relationship of the left precuneus activation (during cued inhibition) with PANSS scores suggests that processing of a complex predictive stimulus (starting at a sensory/perceptual level) is particularly effortful in positive symptom SZ. Previous investigations have demonstrated that those with predominantly positive symptoms struggle most when difficulty increases (Gabel and Ulrich, 1987). Based on these findings it is not surprising to observe

that those with heightened positive symptomatology utilize greater perceptual processing resources. When more attention and effort are required, individuals with positive subsyndrome SZ are likely to suffer from endogenous demands (i.e., hallucinations and delusions) that compete with complex stimuli processing required for adequate task performance (i.e., cues). Taken together, our results provide further evidence for the role of the parietal cortex in cue recognition and inhibition in healthy functioning and further suggest difficulty with such processes in SZ, especially those with positive-dominant symptomatology.

We have interpreted our findings to suggest that the SZ group present inhibitory deficits reflected in d' differences and hypoactivation in cognitive control areas. In addition (perhaps, in a compensatory fashion to achieve healthy levels of performance) individuals with SZ required greater resources in dealing with complex (cued) stimuli. This is evidenced by increased RT following a Nogo trial and heightened activation in the parietal lobe/precuneus during both cues and cued inhibition processing. The SZ group consisted mostly of individuals of the paranoid subtype, known for elevated suspiciousness and hypervigilance (Green and Phillips, 2004), qualities consistent with increased vigilance toward cues. While the observed brain activation patterns are consistent with this hypothesis, however, using performance accuracy-matched groups prevents behavioral Go/Nogo data from providing additional evidence of inhibitory difficulties. In order to assess inhibition without the effect of cues, individuals from both groups performed the CWIT (Delis et al., 2001), in which C3 and C4 subscales require inhibition (i.e., reading color–name words printed in incongruently colored ink, such as “red” printed in blue ink). Despite healthy performance levels in the cued Go/Nogo task, SZ individuals performed more poorly than HC on these two subparts of the CWIT. Furthermore, there was a positive correlation between C3 scores (higher meaning better inhibition) and DLPFC activation for all subjects during inhibition. Since SZ individuals presented deficient inhibitory performance on C3, which was correlated (for all subjects) with the attenuated inhibition-related DLPFC activity, our results confirm the important role of this prefrontal structure during inhibition and further confirm its deficient functioning in SZ. C4 scores (inhibition-switching) were not significantly correlated, possibly because while C3 demands one consistent strategy (i.e., inhibition), C4 also requires numerous strategy switches, confounding inhibitory processes with strategy-switching ones.

This investigation had several limitations. First, the majority of our SZ subjects were medicated with atypical antipsychotics, which are associated with higher levels of neural activity than typical antipsychotics (Braus et al., 2002). This limitation may be precluded by our findings of lower rather than higher levels of dACC and DLPFC activation in the SZ group during the Nogo–Go contrast. A second limitation involves the observed relationship between parietal activation and symptomatology. These findings should be considered with caution since they could be state- rather than trait-dependent. Third, matching groups on performance accuracy leads to a biased sample of SZ individuals, most of whom were diagnosed as paranoid. While this limits generalizability, it is an inevitable consequence of studying compensated performance. Finally, the difference between cue frequency conditions may have been too modest, explaining the lack of associated findings. While these conditions produced significant effects in pilot testing with healthy subjects, more distinct conditions may be necessary to produce reliable differences.

In summary, we examined inhibition processing, cue processing, and the effect of cueing on inhibition (cued inhibition). We compared SZ and HC groups matched for overall task performance accuracy and found that the former presented diminished activation in the DLPFC and dACC during inhibition but greater activation in the inferior frontal gyrus and parietal cortex during cues and cued inhibition, respectively. These results suggest that even SZ individuals performing on par with HC presented hypoactivation in the dACC during inhibition as a result of cognitive control deficits. Furthermore, our results highlight the importance of the parietal cortex in signaling upcoming action withdrawal and suggest difficulties in processing complex stimuli in the SZ group reflected in differences in RT, greater parietal activation (between groups) as well as greater dACC and insula activation (within group). Both deficiencies (i.e., difficulties with inhibition and cue processing) displayed in this paradigm may relate to core deficits in cognitive control and stimulus processing in SZ. Finally, the relationship between heightened parietal cortex with positive symptoms and cue processing during inhibition provides added insight into the etiology of the difficulties this population presents when processing complex cues. Social skills training might emphasize top–down modulation of environmental cue processing that announce the suppression of an automatic action, such as planning for stopping when the yellow light announces the appearance of a red light.

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