Acquiring and Inhibiting Prepotent Responses in Schizophrenia

Event-Related Brain Potentials and Functional Magnetic Resonance Imaging

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Background: Schizophrenia is associated with deficits in using context to establish prepotent responses in complex paradigms and failures to inhibit prepotent responses once established.

Objective: To assess prepotent response establishment and inhibition in patients with schizophrenia using event-related brain potential (ERP) and functional magnetic resonance imaging (fMRI) in a simple NoGo task. To combine fMRI and ERP data to focus on fMRI activations associated with the brief (approximately 200 ms) moment of context updating reflected in the NoGo P300 ERP component.

Design and Setting: We collected ERP and fMRI data while subjects performed a NoGo task requiring a speedy button press to X stimuli (P=.88) but not to K stimuli (P=.12). The ERPs were collected at the Veterans Affairs Palo Alto Health Care System, Palo Alto, Calif; fMRIs were collected at Stanford University, Stanford, Calif.

Participants: We recruited patients with *DSM-IV* schizophrenia (n=11) from the community and the VA hospital and sex- and age-matched healthy control subjects (n=11) from the community.

Main Outcome Measures: Behavioral accuracy, P300 amplitudes and latencies, and fMRI activations suggested that patients with schizophrenia did not establish as strong a prepotent tendency to respond to the Go stimulus as healthy subjects. In healthy subjects, NoGo P300 was related to activations in the anterior cingulate cortex, dorsal lateral prefrontal cortex, and right inferior parietal lobule and caudate nucleus, perhaps reflecting conflict experienced when withholding a response, control needed to inhibit a response, and stopping a response in action, respectively. In patients with schizophrenia, NoGo P300 was modestly related to activations in the anterior cingulate cortex, which is consistent with experiencing conflict.

Conclusions: The difference in ERP and fMRI responses to Go and NoGo stimuli suggested that inhibiting a response was easier for patients with schizophrenia than for healthy subjects. Correlations of P300 and fMRI data suggested that patients with schizophrenia and healthy subjects used different neural structures to inhibit responses, with healthy subjects using a more complex system.

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SCHIZOPHRENIA HAS BEEN ASSOciated with failures of inhibitory control in some but not all experimental tasks. Tasks in which prepotent responses are reflexive, overlearned, or automatic consistently reveal response inhibition deficits in patients with schizophrenia. For example, when the reflex to move the eyes toward a light (prosaccade) must be inhibited and the eyes must be willfully moved in the opposite direction (antisaccade), patients with schizophrenia have inordinate difficulty suppressing prosaccades.[1,2] When presented with the word *red* written in green ink during the Stroop color test, patients with schizophrenia have difficulty inhibiting the overlearned tendency to read the word when their task is to name the ink color.[3,4]

When prepotent response biases are newly learned during an experiment, healthy subjects have more difficulty inhibiting these responses than patients with schizophrenia, perhaps because patients with schizophrenia do not use context to acquire prepotent responses as readily, as is the case with the AX version of the continuous performance task.[5-8] The failure to establish new prepotent responses in patients with schizophrenia is not absolute; they have a high rate of perseverative errors on the Wisconsin Card Sorting Task.[9,10] Both tasks involve fairly complex yet very different stimulus-response mapping rules requiring varying degrees of working memory, learning, set-shifting, and response inhibition. Whether patients with schizophrenia show deficits in developing

prepotent response tendencies or in inhibiting them when cognitive demands are minimized can be addressed more simply in a NoGo task where subjects press a button to one stimulus (Go) but not to the other (NoGo). Even in this simple task, patients with schizophrenia sometimes make more false-alarm errors to NoGo stimuli than healthy subjects[11,12] but not always.[13,14] Nevertheless, when combined with brain imaging tools, this task can assess whether patients with schizophrenia establish prepotent response biases and which neural structures are recruited to inhibit these responses.

METHODS OF ASSESSING INHIBITORY CONTROL IN GO/NOGO TASKS

Two in vivo, noninvasive brain-imaging methods can be used to understand neural responses to NoGo stimuli, electrophysiological and hemodynamic. Electrophysiological methods, using electroencephalography, allow real-time measures of neuronal activity with millisecond temporal resolution. Individual electroencephalograms are averaged to produce an event-related potential (ERP) whose components develop and resolve within tens or hundreds of milliseconds. A less direct measure of neural activity is hemodynamic brain imaging, the most common of which is functional magnetic resonance imaging (fMRI). This operates on a much more delayed time scale; depending on age, task, and brain region, it may take up to 16 seconds to develop and resolve.[15] However, it has superior spatial resolution, allowing a more precise delineation of brain structures and circuits activated during specific tasks.

ERP STUDIES OF INHIBITORY CONTROL IN NOGO TASKS

The ERP has been used for many years to study inhibition of prepotent responses.[16] At approximately 400 ms following a NoGo stimuli, a positive ERP component lasting about 200 ms peaks; it is called the NoGo P300. The Go and NoGo P300s both may reflect context updating[17] necessary for successful ongoing execution and inhibition of prepotent responses. When context has been established to respond to almost every trial (Go), the context does not need to be updated until an exception to the context is presented (NoGo), resulting in a relatively small Go P300 and a large NoGo P300. However, if context to respond or "go" has not been established, relatively large Go P300s and relatively small NoGo P300s will be elicited.

Although associated with sensorimotor inhibition,[18] NoGo P300 cannot be a direct reflection of motor inhibition; it is elicited by NoCount stimuli that are equiprobable with Count stimuli,[16] and it is unaffected by motor response priming.[19]

Although a NoGo P300 is elicited when Go and NoGo stimuli are equiprobable,[20] probability affects NoGo P300 in the same way it affects the Go P300. The more improbable the NoGo stimulus, the larger the NoGo P300 amplitude,[21] reflecting the prepotency of the Go response and the difficulty inhibiting it. An improbable Go (target) stimulus elicits a large P300 with a parietal maximum, whereas an equally improbable NoGo stimulus elicits a P300 with a central frontal scalp distribution.[22]

Because of its association with frontal lobe function and because patients with schizophrenia are known to have wide-reaching functional and structural frontal lobe deficits,[23-25] NoGo P300s should be affected by schizophrenia. Surprisingly, few NoGo ERP studies have been done on patients with schizophrenia. These have had varying degrees of success, perhaps because of the peculiarities of the population studied,[12] the stimulation and acquisition parameters,[11] and demands on working memory.[26]

HEMODYNAMIC STUDIES OF INHIBITORY CONTROL IN NOGO TASKS

While there are many fMRI studies of inhibitory control broadly defined, there are relatively few studies using a simple NoGo paradigm. However, among the studies reported, there is remarkable concordance in confirming the ERP literature that preceded them. NoGo stimuli activate frontal lobe structures including the anterior cingulate cortex (ACC),[20,27-29] premotor cortex,[20,27,28] dorsolateral prefrontal cortex (DLPFC),[4,20,27-30] and posterior right frontal inferior cortex.[31] Right hemisphere structures are more activated than left, particularly in the middle and inferior frontal gyri, frontal limbic area, anterior insula, and inferior parietal lobule (IPL).[32] In addition, caudate nucleus activation[28] and temporal,[4,20,30] parietal,[4,20,27,28] and visual[4,27,30] cortical activations have been noted. Some of these fMRI findings may be affected by the inclusion of errors when block designs were used for analysis[27,28] and by the inclusion of low-probability events.[4,20] Although eliminating error trials is important, balancing probabilities between Go and NoGo stimuli works against the processes we most want to understand: the establishment of prepotent responses and their successful inhibition.

Few NoGo studies using fMRI have been done in patients with schizophrenia. Although patients performed normally in NoGo and Stop signal tasks, they showed reduced activation in the left ACC during both tasks and reduced left rostral DLPFC activation during the Stop task.[13] However, because error trials were included in the analysis and because patients with schizophrenia have different neural responses to errors,[5,33,34] these findings may not be specific to schizophrenia-related differences in response inhibition.

GOALS OF THIS EXPERIMENT

To maximally engage executive control, we attempted to establish a strong prepotent bias to respond to Go stimuli. To build up expectancy for Go stimuli, we skewed stimulus probabilities (Go stimuli=88%; NoGo stimuli=12%), a manipulation that has proved successful in activating frontal lobe structures associated with executive control in other response inhibition tasks.[35] In addition, we pretrained subjects to respond to the stimulus that subsequently became the NoGo stimulus, and we emphasized speed rather than accuracy.

Hemodynamic activity associated with NoGo stimuli is likely to reflect many processes including sensation, perception, attention, response selection, response inhibition, response monitoring, self-evaluation, planning for the next trial, and any number of other processes happening

Variable	Healthy Subjects (n = 11)	Patients With Schizophrenia (n = 11)	P Value
Age, y†	37.30 ± 10 (26-55)	38 ± 13 (23-68)	.90
Education, y†	18.50 ± 2.7 (14.0-22.0)	12.8 ± 3.4 (5.0-19.0)	<.004
Parental socioeconomic status[37]†	31.80 ± 10.4 (12.0-44.0)	37.0 ± 15.5 (16.0-62.0)	.37
BPRS total score, ERP session†‡	NA	39.4 ± 9.6 (19.0-51.5)	
BPRS total score, fMRI session†	NA	41.1 ± 9.5 (20.0-51.5)	
Illness duration, y†	NA	17.30 ± 13.9 (3.0-47.0)	
Handedness[38]	11 Right-handed	9 Right-handed; 1 left-handed; 1 ambidextrous	
Sex	8 Men; 3 women	8 Men; 3 women	
Diagnostic schizophrenia subtype	NA	6 Undifferentiated; 4 paranoid; 1 residual	
Antipsychotic medications	NA	10 Atypical§; 1 typical‖	
Hospitalization status	NA	1 Inpatient; 10 outpatients	

Abbreviations: BPRS, Brief Psychiatric Rating Scale; ERP, event-related brain potential; fMRI, functional magnetic resonance imaging; NA, not applicable.

*Values are expressed as number of individuals unless otherwise indicated.

†Values are expressed as mean ± SD (range).

‡Of the 22 testing sessions for the 11 patients with schizophrenia, symptom ratings and testing (ERP or fMRI) were done on the same day (n = 15) or within 1 (n = 1), 2 (n = 2), 3 (n = 2), 4 (n = 1), or 5 days (n = 1) of each other. Except on 2 occasions, ratings were averaged across 2 raters. Because of the close proximity of ERP and fMRI testing (2 days or less), symptom ratings associated with ERP and fMRI testing were only done once for 5 patients.

§Olanzapine, risperidone, clozapine, quetiapine fumarate.

‖Fluphenazine hydrochloride.

in the 4 to 8 seconds it takes for the hemodynamic response to peak and the subsequent 6 to 8 seconds it takes to return to its baseline state. To focus on fMRI activations in those brain regions associated with context updating, we combined NoGo P300 data with NoGo fMRI data recorded from the same subjects in the same paradigm.

PREDICTIONS

We predicted that patients with schizophrenia would have a smaller difference between NoGo and Go P300s than healthy subjects and a smaller difference between NoGo and Go fMRI activations.[12,13] Whether this was related to reduced neural activity subserving response inhibition to NoGo stimuli or excessive neural activity subserving response execution to Go stimuli was assessed by separate analyses of Go and NoGo responses. Compared with healthy control subjects, we predicted that Go stimuli would be associated with greater effort than NoGo stimuli in patients with schizophrenia owing to their deficient use of context to establish prepotent response tendencies. Thus, we expected patients with schizophrenia would exhibit relatively more omission than false-alarm errors, relatively larger Go than NoGo P300s, and greater fMRI activation to Go than NoGo stimuli. Finally, by correlating NoGo P300 and NoGo fMRI data, we focused on fMRI activations associated with the brief moment (approximately 200 milliseconds) associated with context updating.

METHODS

PARTICIPANTS

In separate sessions, we recorded ERP and fMRI data while 11 patients with *DSM-IV*[36] schizophrenia and 11 healthy comparison subjects performed a NoGo task. All gave written informed consent after the procedures had been fully described. Demographic and clinical data are included in **Table 1.**[37,38]

Patients with schizophrenia were recruited from community mental health centers, as well as from inpatient and outpatient services of the Palo Alto Veterans Affairs Healthcare System, Palo Alto, Calif. All patients with schizophrenia, who were taking stable doses of antipsychotic medications, met *DSM-IV* criteria for schizophrenia based either on the diagnosis from a Structured Clinical Interview for *DSM-IV* conducted by a psychiatrist or psychologist or by consensus of a Structured Clinical Interview for *DSM-IV* conducted by a trained research assistant and a clinical interview by a psychiatrist or psychologist. In 1 case, a psychiatrist made the diagnosis by reviewing the patient's medical record. Prospective patient and control participants were excluded if they met *DSM-IV* criteria for alcohol or drug abuse within 30 days prior to the study. In addition, patient and control participants were excluded for significant head injury and neurological or other medical illnesses compromising the central nervous system. Patient symptoms were assessed using the 18-item Brief Psychiatric Rating Scale.[39,40]

Comparison subjects were recruited by newspaper advertisements and word of mouth, screened by telephone using questions from the Structured Clinical Interview for *DSM-IV*,[41] and excluded for any significant history of Axis I psychiatric illness.

STIMULUS SEQUENCE

Subjects viewed an irregular sequence of K (12%) and X (88%) stimuli, presented for 100 milliseconds each. The stimulus onset asynchrony was 1, 2, or 3 seconds, with each occurring with equal probability. The interval between 2 K stimuli varied between 7 and 24 seconds.[30]

ERP AND fMRI TASK

Participants lifted a lever attached to the index finger of their response hand each time an X stimulus was presented and withheld responding to any K stimuli. There were 42 K stimuli and 288 X stimuli. (Because of a PsyScope [software developed by Cohen et al[42]] buffer error, the last third of the trials in the fMRI environment were presented at a constant 2-second interstimulus interval. These trials were omitted from the analysis of the fMRI data. The same error was not present in the ERP environment

where the stimulus presentation was controlled by STIM software in Neuroscan [Neuroscan, El Paso, Tex.]) To increase the prepotent tendency to respond to K stimuli, we pretrained subjects to respond to K stimuli and not X stimuli in an oddball target detection task. Subjects were told to go as fast as possible and if they made errors, to keep going and not slow down. All but 1 subject made right-handed responses. (All subjects responded with their right hands except for the left-handed patient. The results of the analysis were not changed when she was eliminated from the analysis. Because of considerations of power, her data have been included in the analysis presented herein.)

BEHAVIORAL DATA ACQUISITION, PROCESSING, AND ANALYSIS

A pressure-sensitive piezoelectric transducer that produced a continuous measure of response activity and was sensitive to vigor or acceleration of the response was used to record motor responses. Thus, a slow and weak but erroneous response to a K stimulus might register as a response. These trials were eliminated by setting a very low criterion for a motor response (>15% of the rolling average amplitude of 20 surrounding trials). A very brisk but partial response might also register as a response, as could small finger twitches and any pressure changes against the device.

ERP DATA ACQUISITION, PROCESSING, AND ANALYSIS

Participants were seated in a sound-attenuating, electrically shielded booth. Electroencephalography data recorded from the F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4 electrode sites are reported herein. Vertical electrooculogram data were recorded from electrodes placed above and below the right eye, and horizontal electrooculogram data were recorded from electrodes placed at the outer canthus of each eye. Data were sampled at 500 Hz and bandpass filtered at 0.05 to 30 Hz.

Before baseline correction, single-trials were corrected for eye blink and eye movement artifacts based on correlations between electroencephalograms recorded at each electrode site and vertical and horizontal electrooculograms[43]. Trials exceeding +100 µV were then rejected. The linear component of each averaged ERP from −100 to 1000 milliseconds was removed before peaks were identified and measured. Only trials with correct responses to X stimuli or successful inhibition of responses to K stimuli were included in the ERPs.

The P300 peak was identified as the maximum positive voltage between 280 and 600 milliseconds. Its amplitude was quantified as the average voltage around the peak (+50 milliseconds) relative to a 100 milliseconds prestimulus baseline. Before P300 was measured, data were low-pass filtered at 12 Hz.

Univariate repeated-measures analyses of variance were performed for P300 amplitude and latency for the following factors: group (comparison subjects, patients with schizophrenia), stimulus (K stimulus vs X stimulus), anterior posterior scalp site (frontal, central, parietal), and lateral scalp site (left, middle, right).

fMRI DATA ACQUISITION, PROCESSING, AND ANALYSIS

Images were acquired on a GE 3 Tesla magnetic resonance imaging scanner (General Electric, Milwaukee, Wis) using a custom-made head coil with a spiral gradient echo sequence.[44] Subjects were stabilized with a bite bar made from their dental impression.

Image processing was performed with statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, London, England).

Rests (the first and last 14 trials) and trials associated with a PsyScope buffer error were not included in this analysis. X stimuli hits, X stimuli omissions, K stimuli successful inhibitions, and K stimuli false alarms were modeled for all but the 5 subjects who had no X stimuli omissions. Analyses were done in 2 stages. First, per subject per voxel β estimates were computed, producing brain maps of parameters for all of the explanatory variables. Second, a random-effects model was applied to individual subject images derived during first-level analyses separately for healthy subjects and patients with schizophrenia. Specific responses to Go and NoGo stimuli were assessed by separate examination of Go and NoGo β images (reflecting the peak amplitude of the fitted hemodynamic response), and group contrasts for Go and NoGo β images were each performed separately. In addition, NoGo-Go and Go-NoGo contrasts were estimated separately for patients with schizophrenia and healthy subjects, using 2-sample t tests. Group contrasts of these contrasts were also estimated.

We correlated NoGo fMRI values at each voxel with the NoGo P300 amplitude at Fz, Cz, and Pz electrode sites entered as the covariate in the simple regression option in SPM99. This was done separately for both groups.

RESULTS

BEHAVIORAL PERFORMANCE

As presented in **Table 2**, patients with schizophrenia had a higher overall error rate than healthy subjects. Across ERP and fMRI, patients with schizophrenia made a lower percentage of false-alarm errors to NoGo stimuli than healthy subjects (50.4% vs 68.2%) and a higher percentage of omission errors to Go stimuli, which is consistent with a failure to form a strong prepotent bias to respond to Go stimuli. Poorer performance during fMRI than ERP could be due to fMRI testing preceding ERP testing for most of the subjects or to the awkward posture, restriction of movement, ambient noise, and anxiety associated with fMRI.

EVENT-RELATED BRAIN POTENTIALS

The ERPs to Go and NoGo stimuli are shown in **Figure 1**. (Apparent group X stimulus differences in the N1 and N2 ERP components were not significant, which is consistent with other comparisons of patients with schizophrenia and control subjects in NoGo tasks [Kiehl et al[12]].) P300 areas were compared in a 4-way analysis of variance for stimulus, anterior posterior scalp site, laterality, and group (**Table 3**). There was a significant main effect of stimulus ($F_{1,20}$=30.84; P<.001) with NoGo stimuli eliciting larger P300s across all scalp sites than Go stimuli, and there was an interaction of group X stimulus ($F_{1,20}$=5.14; P<.04) reflecting a smaller stimulus effect in patients with schizophrenia (2.4 µV) than in healthy subjects (5.7 µV). To determine whether the reduced NoGo-Go effect in patients with schizophrenia was due to larger P300s to Go or smaller P300s to NoGo, the group effect was assessed for Go and NoGo P300 separately. While Go P300 was larger in patients with schizophrenia (4.8 µV) than in healthy subjects (3.4 µV) ($F_{1,20}$=1.47; P=.24) and NoGo P300 was smaller in patients with schizophrenia (7.2 µV) than in healthy subjects (9.1 µV) ($F_{1,20}$=1.03; P=.32), neither was significant.

To determine whether reduced NoGo-Go P300 amplitude differences seen in patients with schizophrenia could be attributed to symptom severity, they were regressed against total Brief Psychiatric Rating Scale score. Fewer symptomatic patients with schizophrenia had larger NoGo-Go P300 differences ($r = -0.62$; $P < .04$), suggesting that clinical severity contributed to attenuated differences in NoGo vs Go stimulus processing.

Analysis of variance of P300 latencies revealed a significant group effect ($F_{1,20} = 6.23$; $P < .03$) with P300 being earlier in healthy subjects than in patients with schizophrenia and a significant stimulus effect ($F_{1,20} = 19.38$; $P < .001$) with P300 being later to NoGo (461 ms) than to Go (411 ms) stimuli (Table 3). Importantly, there was a trend toward a significant group X stimulus interaction ($F_{1,20} = 4.11$; $P < .06$) due to the larger difference between Go and NoGo responses in healthy subjects (73 ms) than in patients with schizophrenia (27 ms), again suggesting that patients with schizophrenia responded more similarly to Go and NoGo stimuli.

fMRI

No activated voxels reached a corrected significance level of $P < .05$ when adjusted for the entire volume for the NoGo-Go contrast. Instead, we used a height threshold of $P < .01$ (uncorrected) and an extent threshold of 6. Significant gray matter voxel–level activations are reported. (To determine if patients with schizophrenia moved more than comparison subjects, as has sometimes been reported,[45] movement parameters derived during the realignment step of the analysis were compared in two 2-way analyses of variance for group and dimension [one analysis X, Y, Z and one for pitch, roll, yaw]. Movements in the Z plane were significantly greater than in the X and Y planes [$P < .001$], but none of the movements was affected by group.)

COMPARISON SUBJECTS

Contrast Images

Many brain regions were more activated to NoGo than Go stimuli in healthy control subjects, reflecting a combination of response conflict, response inhibition, stimulus improbability, and task relevance (eg, DLPFC, ACC, IPL, basal ganglia), particularly in the right hemisphere. These can be seen in Figure 1 and are listed in **Table 4.**[46] To understand which brain regions were more active to Go than NoGo stimuli, the Go-NoGo contrast was estimated. No voxels survived our threshold, indicating healthy control subjects expended very little neural energy making the automatic prepotent response to Go stimuli relative to inhibiting responses to NoGo stimuli. When we dropped the threshold to $P < .05$, activations were seen in the left somatosensory cortex, confirming motor response involvement.

β Images

That there was greater activation to NoGo than to Go stimuli is also reflected in the β images (Figure 1) (Table 4), which indicate activated voxels with β values signifi-

Table 2. Accuracy Means and Analysis of Variance Results

	Mean ± SD
Percentage of Errors*	
fMRI environment	
Healthy subjects	7.2 ± 2.0
Patients with schizophrenia	10.5 ± 5.8
ERP environment	
Healthy subjects	12.5 ± 3.1
Patients with schizophrenia	18.6 ± 11.0
Percentage of Omitted Responses†	
fMRI environment	
Healthy subjects	0.7 ± 1.5
Patients with schizophrenia	4.5 ± 5.4
ERP environment	
Healthy subjects	8.8 ± 5.7
Patients with schizophrenia	16.2 ± 13.3
Percentage of False Alarms (Adjusted for Error Rate)‡	
fMRI environment	
Healthy subjects	92.5 ± 13.3
Patients with schizophrenia	67.9 ± 24.6
ERP environment	
Healthy subjects	43.9 ± 30.0
Patients with schizophrenia	32.9 ± 23.0

Abbreviations: ERP, event-related brain potential; fMRI, functional magnetic resonance imaging.

*Percentage of total errors = ([false alarms to K stimuli + omitted responses to X stimuli]/total trials [X stimuli + K stimuli]) × 100. Group: $F_{1,20} = 4.05$, $P < .058$; environment: $F_{1,20} = 20.64$, $P < .001$; group × environment: $F_{1,20} = 0.90$, $P = .35$.

†Percentage of omitted responses = (omitted responses to X stimuli/total X stimuli trials) × 100. Group: $F_{1,20} = 4.52$, $P = .05$; environment: $F_{1,20} = 25.60$, $P < .001$; group × environment: $F_{1,20} = 0.89$, $P = .36$.

‡Percentage of false alarms = (false alarms to NoGo stimuli/total errors) × 100. Group: $F_{1,20} = 5.14$, $P < .04$; environment: $F_{1,20} = 45.34$, $P < .001$; group × environment: $F_{1,20} = 1.19$, $P = .29$.

cantly different from zero. NoGo and Go stimuli were associated with activation of 1098 and 100 gray matter voxels, respectively. The majority (66%) of activated voxels to the Go stimulus were in the left somatosensory or motor cortex, reflecting the motor response.

PATIENTS WITH SCHIZOPHRENIA

Contrast Images

The NoGo-Go contrast revealed modest activations (106 gray matter voxels), mostly in the right frontal and parietal cortices (Figure 1) (Table 4). With the reverse contrast (Go-NoGo), 61 gray matter voxels were activated in the patients with schizophrenia, indicating relatively greater recruitment of effortful processes compared with healthy control subjects.

β Images

That there was greater activation to Go (222 gray matter voxels) than NoGo (69 gray matter voxels) stimuli is also reflected in the β images shown in Figure 1. About 33% of voxel activations to the Go stimulus were in the left somatosensory or motor cortex, reflecting the motor response; however, about 60% were in regions associated
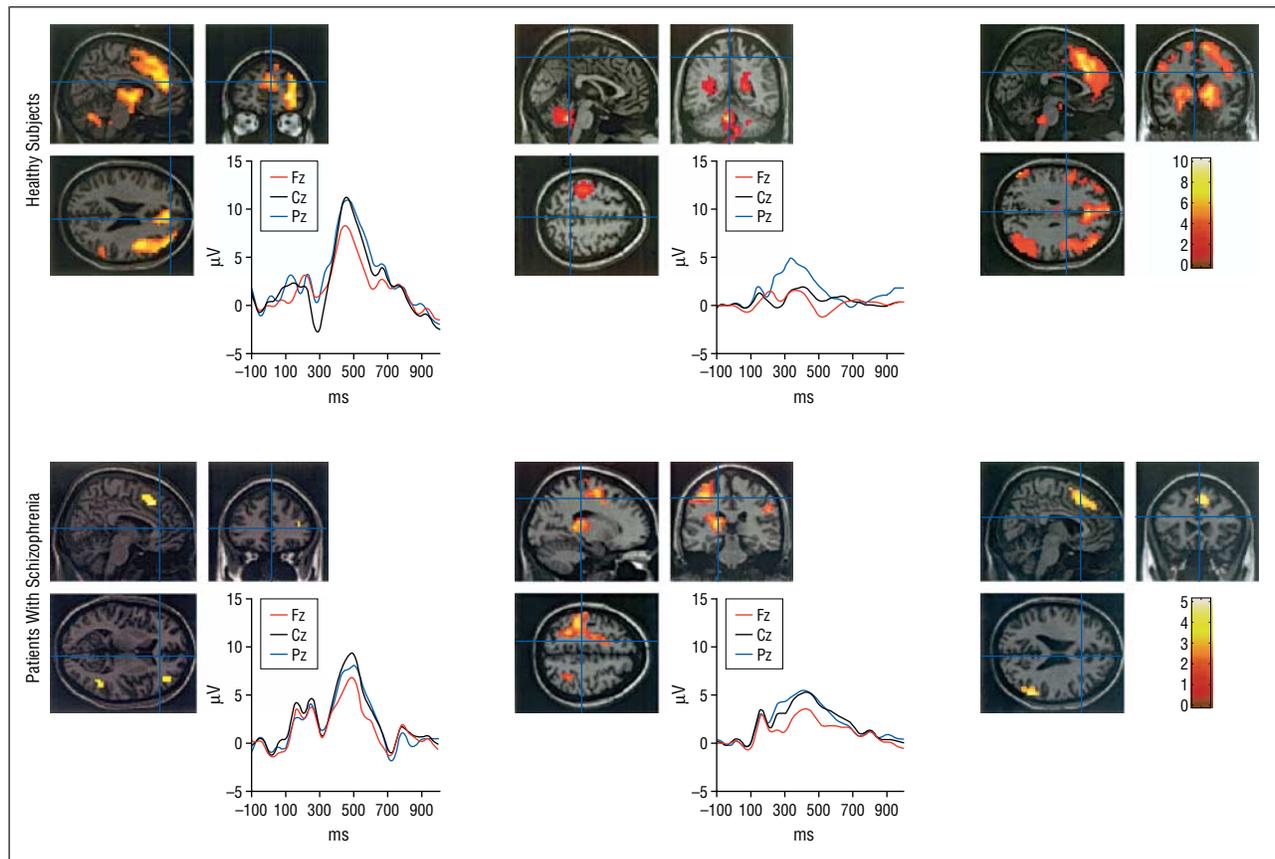
Figure 1. Three planar views of functional magnetic resonance image activations for the β images of NoGo (left) and Go (middle) activations for healthy subjects (upper row) and patients with schizophrenia (lower row). The sections were chosen to illustrate maximal activations on the axial, coronal, and sagittal cuts. The event-related brain potentials (ERPs) from the Fz, Cz, and Pz electrode sites are overlaid for the appropriate β images. The contrast images for NoGo-Go activations are shown on the right. Positivity in the ERPs is plotted up. Images on right of the figure are from the right side of the brain.

Table 3. Means for P300 Amplitude and Latency*

Variable	Healthy Subjects	Patients With Schizophrenia
P300 Amplitude, μV		
NoGo (K stimuli)		
Anterior posterior scalp site		
Frontal	8.23 ± 0.69	6.96 ± 1.11
Central	9.63 ± 0.95	7.68 ± 0.86
Parietal	9.34 ± 0.70	6.93 ± 0.87
Go (X stimuli)		
Anterior posterior scalp site		
Frontal	2.53 ± 0.36	4.53 ± 0.85
Central	3.29 ± 0.61	4.93 ± 0.55
Parietal	4.42 ± 0.41	4.98 ± 0.53
P300 Latency, ms		
NoGo (K stimuli)	453 ± 5.88	469 ± 5.54
Go (X stimuli)	380 ± 6.76	442 ± 6.92
No. of Trials Included in ERPs		
NoGo (K stimuli)	24.55 ± 2.75	23.82 ± 2.39
Go (X stimuli)	260.46 ± 5.27	215.46 ± 15.64

Abbreviation: ERP, event-related brain potential.
*Values are expressed as mean ± SE.

with target detection (frontal, temporal, and parietal lobes, and insula and thalamus).

GROUP COMPARISONS

Contrast Images

As presented in Table 4, healthy control subjects had greater activations than patients with schizophrenia for the NoGo-Go contrast, predominantly in brain regions activated in healthy subjects. No voxels were more activated in patients with schizophrenia than healthy subjects for this contrast. With the reverse contrast (Go-NoGo), patients with schizophrenia had greater activations than healthy control subjects, with 177 gray matter voxels being activated in the somatosensory and motor cortex, ACC, DLPFC, striatum, and insula. No voxels were more activated in control subjects than patients with schizophrenia for this contrast.

β Images

β images to NoGo stimuli were contrasted for patients with schizophrenia and healthy subjects (Table 4). Healthy subjects had significantly more activation than patients with schizophrenia, but no voxels were more activated in patients with schizophrenia than healthy subjects for this contrast.

β images to Go stimuli were contrasted for patients with schizophrenia and healthy subjects (Table 4). Patients with schizophrenia had significantly more activa-

Table 4. Regions and Brodmann Areas (BAs)*

	No Go-Go Contrast Images						NoGo β Images						Go β Images					
	HCS		SZ		HCS-SZ†		HCS		SZ		HCS-SZ†		HCS		SZ		SZ-HCS‡	
Region	BAs	N	BAs	N	BAs	N	BAs	N	BAs	N	BAs	N	BAs	N	BAs	N	BAs	N
Left hemisphere																		
Inferior frontal gyrus	13, 45, 47, 6, 9	35			9	1	13, 44, 45, 47	22							44, 47	4		
Medial frontal gyrus	6, 8, 9, 10	74			6, 8, 9, 32	10	6, 8, 9, 10	34							6, 32	6		
Middle frontal gyrus	6, 8, 9, 10	41			10	6	8, 9	5							6	10		
Superior frontal gyrus	6, 8, 9, 10	68			6, 10	3	6, 8	19										
Paracentral gyrus					5	4												
Gyrus precentralis	6, 9, 44	24			4, 6, 13, 43	7	4, 44	15					4, 6	40	4, 6, 44	60		
Subgyral frontal lobe	8	1			8	1									6	4		
Anterior cingulate cortex	24, 32, 42	40			24, 32	4	32, 42	3										
Cingulate gyrus	23, 32	18			24, 31, 32	19	24, 32	6	32	2					32	1		
Parahippocampus	AMYG, HC, 34	12					HC, AMYG, 34	14			AMYG, 34	5						
Subcallosal gyrus	34	1																
Uncus	AMYG	1																
Middle occipital gyrus	18, 19, 37	18			18, 19	2	19, 37	3			19	1						
Inferior occipital gyrus	18, 19	3																
Superior occipital gyrus	19	4			19	1												
Cuneus	17	8			19	21												
Gyrus lingualis	17, 18	6																
Inferior parietal lobe			40	1	40	12			40	8			40	1	2, 4	14		
Superior parietal lobe	7	7			7	2			7	2								
Gyrus supramarginalis	39, 40	6	40	1	40	5												
Gyrus postcentralis					2, 3, 40, 43	17	2, 3	8					2, 3, 40	26	4	1		
Precuneus					7, 19	15												
Gyrus fusiformus	20	1					20	2										
Inferior temporal gyrus							37	1										
Middle temporal gyrus	19, 37, 39	16			21	2					19, 37, 39	4						
Superior temporal gyrus	22, 38, 39	22			22, 42, 38	16	38	7			38, 39	3	29, 41	7	22	8		
Transverse gyrus					42	1							41	2				
Subgyral temporal lobe	20	1					20	2										
Nucleus lentiformis, GP		24		2		1		16				4						
Nucleus lentiformis, putamen		75		13		2		62				4						
Nucleus lentiformis		2						2				2						
Thalamus		4						30						5		12		15
Caudatus nucleus	Body, head	4											Tail	4	Tail	1	Tail	3
Insula	13, 47	14			13	11	13, 47	13					13, 29, 40	8	13	17		
Claustrum		11						9										
Sublobar extranuclear	13	1					13, 47	2										
Left Hemisphere Total		542		17		162		275		13		19		93		138		18

(continued)

tion than healthy subjects in the thalamus, IPL, and caudate nucleus. Only 2 voxels (in Brodmann area 8) were more activated in healthy subjects than patients with schizophrenia for this contrast.

ERP and fMRI Correlations

In healthy subjects, larger NoGo P300s were associated with greater NoGo fMRI activations centered in the ACC, DLPFC, IPL, and caudate nucleus, depending on the ERP electrode site (**Figure 2**). In patients with schizophre-

nia, the same analysis revealed modest correlations in the ACC for NoGo P300 recorded from the Pz electrode site (**Figure 3**).

COMMENT

BEHAVIORAL DATA

Our intention was to establish a strong prepotent tendency to respond on every trial, thereby increasing the difficulty of response inhibition to infrequently occur-

Table 4. Regions and Brodmann Areas (BAs)* (cont)

Region	No Go-Go Contrast Images						NoGo β Images						Go β Images					
	HCS		SZ		HCS-SZ†		HCS		SZ		HCS-SZ†		HCS		SZ		SZ-HCS‡	
	BAs	N	BAs	N	BAs	N	BAs	N	BAs	N	BAs	N	BAs	N	BAs	N	BAs	N
Region (cont)																		
Right hemisphere																		
Inferior frontal gyrus	6, 9, 13, 44, 45, 46, 47	64	46	1			9, 10, 13, 44, 45, 46, 47	91	46, 47	8					13, 44, 45, 47	23		
Medial frontal gyrus	6, 8, 9, 10, 32	92	6, 8	11	6, 32	11	6, 8, 9, 10, 32	75	8	6								
Middle frontal gyrus	6, 8, 9, 10, 46	124	10	1			6, 8, 9, 10, 11, 46, 47	97	10, 46	4								
Superior frontal gyrus	6, 8, 9, 10, 11	111	6, 8	3	6	5	6, 8, 9, 10, 11	77										
Gyrus precentralis	4, 6, 9, 44	41			43	1	6, 9, 44	22							44	6		
Subgyral frontal lobe	6, 8	5					6, 10	4							13, 47	7		
Anterior cingulate cortex	10, 24, 32, 42	42			24	2	24, 32, 42	28										
Cingulate gyrus	23, 24, 32	36	32	3	24, 32	9	24, 32	37	32	3			31	3				
Parahippocampus	AMYG	8					AMYG, 34	20										
Middle occipital gyrus	19, 37	2					19	1										
Superior occipital gyrus	19, 39	2			19	2												
Cuneus					19	2												
Inferior parietal lobe	7, 39, 40	61	40	7	40	28	7, 39, 40	64	7, 40	18					40	12	40	7
Superior parietal lobe	7, 40	31	7, 40	3	7	10	7, 40	25	7, 40	5								
Gyrus supramarginalis	40	3	40	4	40	1	40	8	40	1								
Gyrus postcentralis	3	3			2, 3, 7, 40, 43	17					5	3			2	6	2	3
Gyrus angularis	39	11																
Precuneus	7, 19, 39	24	7	1	7, 19	12	19	1	7	5			7	1				
Gyrus fusiformis					19, 37	9												
Subgyral parietal lobe	10	2			37, 40	3												
Inferior temporal gyrus	37	4	20, 37	4														
Middle temporal gyrus	19, 21, 37, 39	26	37, 39	2			21, 37	6	39	1								
Superior temporal gyrus	13, 22, 38, 39	40	13, 22, 39	10	13, 22, 41, 42	10	13, 22, 38	22	13	1					22, 38	8		
Transverse gyrus					41	2												
Subgyral temporal lobe															21	1		
Nucleus lentiformis, GP		35		4		2		34				6						
Nucleus lentiformis, putamen		92		35		3		90				11						
Thalamus		49						67								3		
Nucleus subthalamicus		4						3										
Caudatus nucleus	Body, head, tail	12					Head, body	16										
Insula	13	12					13, 47	26	13, 47	2					13, 47	21		
Claustrum		7										3						
Sublobar extranuclear	AMYG, HYPO, 13	10					13, 47	9	13	2								
Nigra		3																
Red nucleus		1																
Right Hemisphere Total		957		89		129		823		56		23		7		84		10

Abbreviations: AMYG, amygdala; GP, global pallidus; HC, hippocampus; HCS, healthy control subjects; N, number of gray matter voxels; SZ, patients with schizophrenia.

*As described by Lancaster et al.[46] Regions are listed if more than 6 continuous voxels were activated using $P<.01$ (uncorrected) threshold. Number of gray matter voxels activated in each region is listed. fMRI acquisition parameters: Data were acquired in the axial plane oriented parallel to the anterior commissure–posterior commissure line prescribed from the midsagittal slice of a previously acquired spoiled gradient echo pulse anatomical sequence. Twenty-four axial slices (6-mm thick, 0-mm gap) were acquired with each 1.5-second repetition time (echo time = 30 milliseconds; number of signal averages = 1; field of view = 24 cm; flip angle = 70°; bandwidth = 100 kHz; matrix = 64 × 64). Voxel dimensions were 3.75 × 3.75 × 6 mm. Images corresponding to the first 4 repetition times were discarded from further analysis to eliminate nonequilibrium effects. fMRI processing: Functional images were slice-time corrected, reoriented to an origin located at the anterior commissure, and motion corrected to the first scan. The mean functional image was normalized to the MNI Echo-Planar Image (Montreal Neurological Institute, Toronto, Ontario) template using a 12-parameter affine transformation and 4 × 5 × 4 nonlinear basis functions, and the resulting parameters were used to anatomically normalize all individual functional images in the time series. The images were subsequently resliced to 4 × 4 × 4 mm using sinc interpolation and then spatially smoothed with a Gaussian filter, 10-mm full width at half maximum. Smoothing facilitated intersubject averaging by minimizing differences in functional and gyral anatomy, enhanced signal-to-noise ratio, and satisfied assumptions of Gaussian random field theory implemented in SPM99 (Wellcome Department of Cognitive Neurology, London, England). Low-frequency noise was removed with a temporal high-pass filter (cut-off based on statistical parametric mapping defaults), and grand mean scaling was implemented to adjust images for global differences in image intensity across subjects. fMRI analysis: For individual subject analyses, a fixed effects event-related design was implemented using multiple linear regression time series analyses 51 to determine the location and extent of brain activations. Hemodynamic responses were modeled using statistical parametric mapping canonical hemodynamic response function (2 γ functions) with temporal and dispersion derivative terms.

†No gray matter voxels were significantly activated in the reverse contrast (SZ-HCS).

‡Only 2 gray matter voxels in left BA 8 were significantly more activated in the reverse contrast (HCS-SZ).

ring NoGo stimuli in an otherwise cognitively simple NoGo task. Based on the behavioral data, we achieved this goal in healthy subjects who rarely failed to respond to Go stimuli but who often failed to inhibit re-
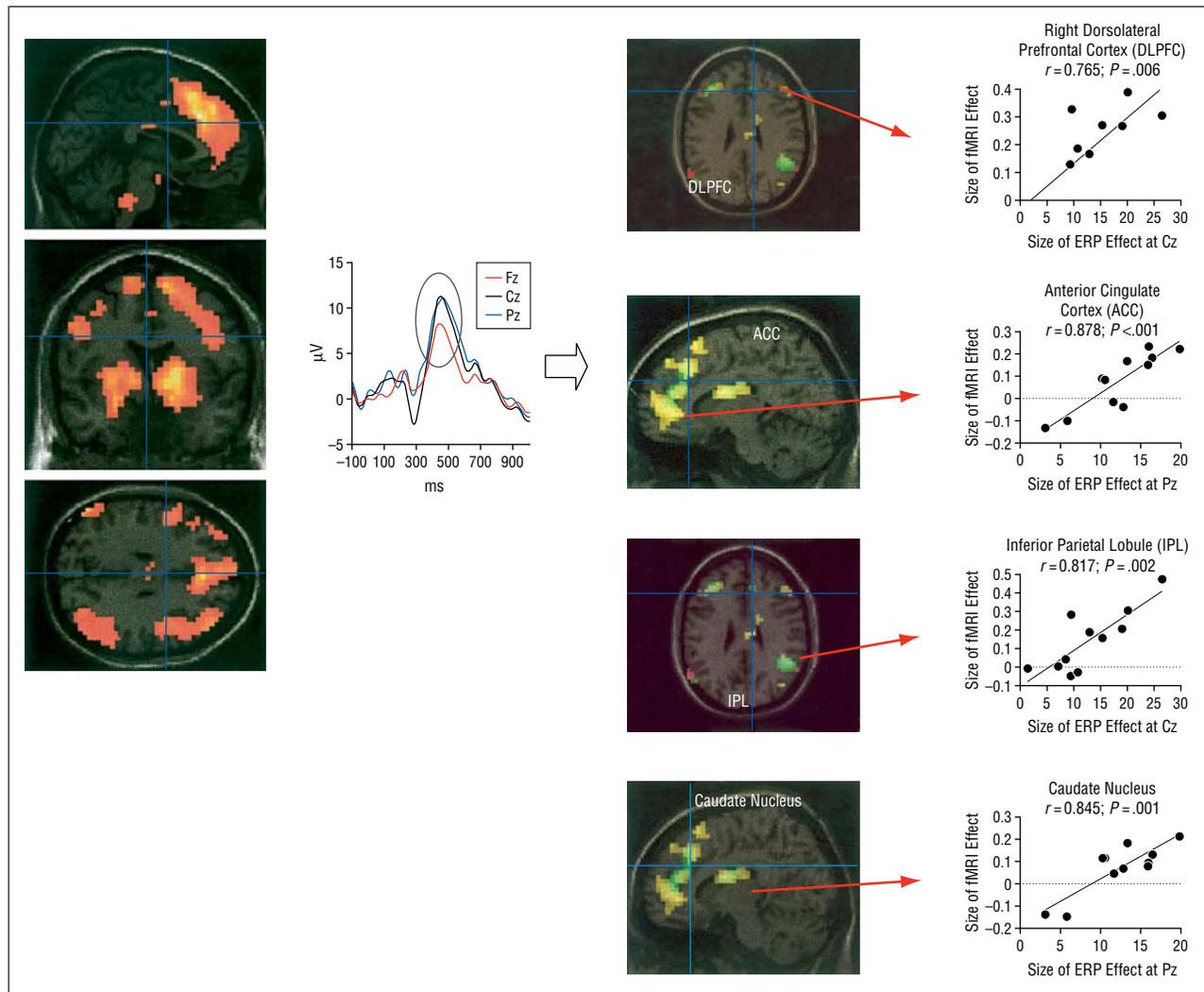
Figure 2. The NoGo functional magnetic resonance imaging (fMRI) β image (left) (approximately 12-16 seconds) and NoGo event-related brain potentials (ERPs) (middle) (P300 lasts approximately 200 milliseconds) for healthy control subjects, as shown in Figure 1. The NoGo P300 is circled. Correlations between fMRI activations and P300 amplitudes (recorded at the Fz [red blobs], Cz [green blobs], and Pz [yellow blobs] electrode sites) appear as activations on the right (*P*<.01 uncorrected; contiguous voxels=6). Scatter plots and correlation coefficients appear on the far right, and fMRI effects represent the average value for that region. Centroids are given in Talairach coordinates (millimeters).

sponses to NoGo stimuli. Patients with schizophrenia did not establish as strong an automatic or prepotent response bias and instead may have fully evaluated each stimulus on each trial, making a deliberate choice to respond or not to respond. This was evident in their greater percentage of omission errors than false-alarm errors, consistent with previous findings by Carter et al,[5] Barch et al,[6] Henik et al,[7] and Servan-Schreiber et al[8] demonstrating that patients with schizophrenia are deficient in the use of context to establish prepotent response biases.

fMRI DATA

As expected, compared with Go stimuli, NoGo stimuli activated more right (957 voxels) than left (474 voxels) hemisphere structures,[31,47] as well as many voxels in the frontal lobe including the ACC,[20,27-29] DLPFC,[4,20,27-30] and inferior frontal cortex.[31] In addition, we confirmed greater temporal lobe,[4,20,30] parietal lobe,[4,20,27,28] and caudate nucleus[28] activations to NoGo compared with Go stimuli. Al-

though ACC activation has also been associated with the commission of errors,[30] because of our extreme measures to eliminate errors and partial errors from the analysis, it is unlikely that ACC involvement in this case reflects the contribution of errors. Instead it may reflect monitoring for conflict and the detection of potential for error[48] or simply the infrequency of the NoGo stimulus.[4] Recent data from Milham et al[49] suggest that the ACC monitors for the presence of competing or conflicting actions in an effort to prevent execution of erroneous motor actions. On detecting conflict, a signal may be sent to the frontal lobe structures to implement top-down executive control to stop the initiation of an inappropriate motor response.[35] In this task, the final effort to stop responses in progress, as observed in Stop signal tasks, may be responsible for both caudate nucleus[27] and IPL activations.[50]

As predicted, patients with schizophrenia had a smaller difference in fMRI activation to NoGo compared with Go stimuli than healthy subjects, although the same brain regions (right frontal and parietal) were
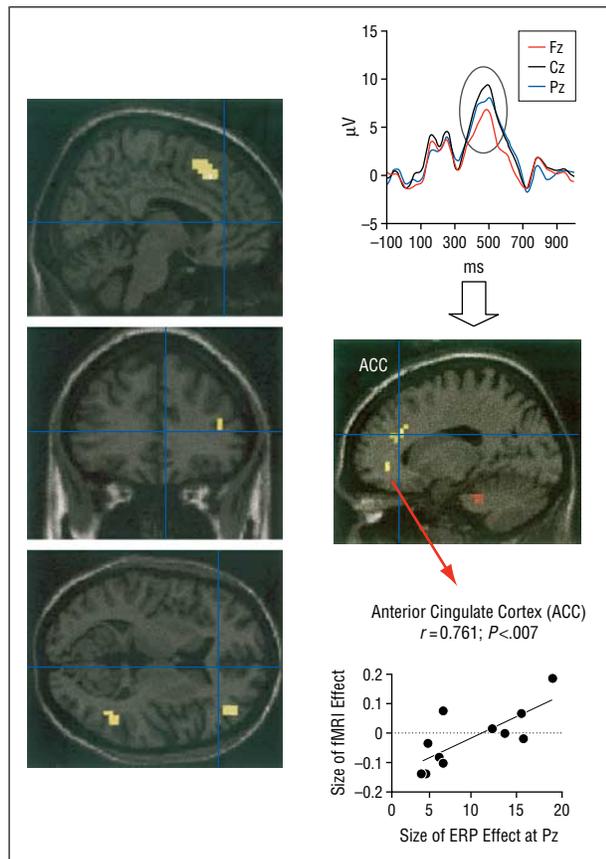
Figure 3. The NoGo functional magnetic resonance imaging (fMRI) β image (left) (approximately 12-16 seconds) and NoGo event-related brain potentials (ERPs) (top right) (P300 lasts approximately 200 milliseconds) for patients with schizophrenia, as shown in Figure 2. The NoGo P300 is circled. Correlations between fMRI activations and P300 amplitudes (recorded at the Fz [red blobs], and Pz [yellow blobs] electrode sites) appear as activations on the middle right ($P<.01$ uncorrected; contiguous voxels=6). A scatter plot and correlation coefficient appear on the lower right, and fMRI effects represent the average value for that region. Centroids are given in Talairach coordinates (millimeters).

activated in both groups. This reduced difference in patients with schizophrenia can be attributed both to greater activation to Go stimuli and less activation to NoGo stimuli, consistent with behavioral data suggesting Go responses were more effortful and deliberate for patients with schizophrenia than healthy subjects and that NoGo responses were not as difficult for patients with schizophrenia to inhibit. Importantly, most of the activations associated with Go stimuli in patients with schizophrenia were in brain regions typically associated with effortful target detection and implicated in generating visual target P300s.[51-53]

ERP DATA

As expected,[21] infrequent NoGo stimuli elicited larger and later P300s than frequent Go stimuli in healthy subjects. Patients with schizophrenia showed less P300 amplitude and latency distinction between NoGo and Go stimuli, suggesting that they processed Go and NoGo stimuli similarly. This represents a relatively new finding. Few NoGo studies have been done in patients with schizophrenia, and those that have been done are difficult to interpret owing

to the peculiarities of populations studied[12] and differences in recording parameters.[11] Importantly, P300 data are consistent with fMRI data in suggesting that reduced differences in patients with schizophrenia were due to both larger Go P300s and smaller NoGo P300s, although neither effect was significant.

ERP AND fMRI CORRELATIONS

The behavioral, fMRI, and ERP data all suggest that the NoGo task engaged different response inhibition strategies in patients with schizophrenia and healthy subjects. This conclusion is underscored by the correlation analysis of ERP and fMRI data, which allowed us to focus narrowly on those brain activations associated with the brief (approximately 200 milliseconds) moment of context updating following a NoGo stimulus. Specifically, correlations between ERP and fMRI data were found in the ACC, DLPFC, caudate nucleus, and right IPL. Healthy subjects with larger NoGo P300 amplitudes had greater NoGo fMRI activations in these brain regions associated with executive control. The sequencing of these structures in the service of response inhibition awaits refinements in methods to detect small temporal differences in fMRI activations. The correlations in patients with schizophrenia were different. Patients with larger NoGo P300s had larger NoGo fMRI activations only in the ACC, suggesting the experience of conflict is associated with the elicitation of the NoGo P300. That patients with schizophrenia who had a more normal pattern of P300s did not have a more normal pattern of fMRI response may reflect their inability to recruit DLPFC, IPL, and striatum, even when a normal strategy is attempted.

While large regions of brain were activated by NoGo stimuli, especially in healthy subjects, very few of these regions were correlated with NoGo P300. Instead, these must subserve processes other than those related to context updating reflected in the NoGo P300 component following response inhibition. This correlational technique does not provide source localization for ERP components but rather capitalizes on individual differences in neural (ERP) and hemodynamic (fMRI) responses, identifying areas of the brain that have greater hemodynamic responses in people who have larger ERPs. Our results suggest that healthy subjects set up prepotent response biases and when responses have to be inhibited, effort must be expended. This ongoing effort, reflected in NoGo P300 amplitude, is associated with the engagement of neural structures associated with executive control. Patients with schizophrenia, however, did not set up strong prepotent response biases, and their NoGo P300s instead reflect the simple experience of conflict associated with ACC activation.

This analysis is an example of how we might start to combine ERP and fMRI data to generate hypotheses about different task strategies used by neuropsychiatric populations and the neural structures recruited to implement them. However, our conclusions are limited by the small sample sizes studied, the low probability threshold used, the fact that patients with schizophrenia were all medicated, and the fact that subjects used their preferred hand for responding. Also, because we did not correct for multiple comparisons, these findings need to be replicated in a new sample.

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