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# Parietal Dysfunction Is Associated with Increased Outcome-Related Decision-Making in Schizophrenia Patients

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**Background:** *Decision-making is a complex process and depends on a network of fronto-parietal and cingulate areas. Decision-making dysfunctions in schizophrenia patients are characterized by an alternation between stereotypic and unpredictable responses. This study tested the hypothesis that schizophrenia patients show less decision-making-related activation in the prefrontal and parietal cortex.*

**Methods:** *Fifteen schizophrenia patients were matched with fifteen normal comparison subjects. During functional magnetic resonance imaging (fMRI) scanning, subjects were tested on the two-choice prediction task (predicting the location of a randomly presented stimulus) and the two-choice response task (responding according to the location of the stimulus).*

**Results:** *Schizophrenia patients relative to comparison subjects generated more outcome-dependent responses. Schizophrenia patients and normal comparison subjects showed decision-making-related activation in right prefrontal cortex, insula, anterior cingulate, and bilateral precuneus. Schizophrenia patients showed less activation in inferior, medial prefrontal, and right superior temporal parietal cortex and more activation in the postcentral and inferior parietal cortex. Decision-making-related activation in both right prefrontal and bilateral parietal cortex was higher in medicated compared to unmedicated schizophrenia patients.*

**Conclusions:** *These results support the hypothesis that the interaction between prefrontal and parietal cortex during decision-making by schizophrenia patients is dysregulated, which results in an increased outcome-dependent response selection. Biol Psychiatry 2002;51:995-1004 © 2002 Society of Biological Psychiatry*

**Key Words:** Decision-making, schizophrenia, fMRI

## Introduction

Schizophrenia affects a complex set of cognitive functions. Among these cognitive functions are problems with decision-making. Specifically, schizophrenia patients alternate between sequences of responses during the two-choice prediction task that are either highly predictable or highly unpredictable (Paulus et al 1996), utilize the stimulus information less than normal comparison subjects, and select actions based on a long history of preceding behavioral responses, yielding extensive correlations across sequences of responses (Paulus et al 1999). These decision-making dysfunctions are independent of psychopathology and are stable over time (Paulus et al 2001b).

Decision-making includes several cognitive and non-cognitive processes, such as attention, working memory (Bechara et al 1998), contingency approximation (Elliott and Dolan 1998; Tversky et al 1988), hypothesis testing (Elliott and Dolan 1998), rule generation (Seale and Rapoport 1997), impulsivity (Green et al 1999; Monterosso and Ainslie 1999), and risk-taking (Rahman et al 1999; Rogers et al 1999a). In addition, decision-making also involves affective factors, such as unconscious hunches (Bechara et al 1998) and anticipated subjective expected pleasure (Mellers et al 1999). Functional neuroimaging studies of decision-making have shown task-related activation in both orbitofrontal (Elliott et al 1999; Rogers et al 1999b) and dorsolateral prefrontal cortex, as well as parietal and cingulate cortex (Elliott and Dolan 1998; Paulus et al 2001a). Therefore, a distributed network of prefrontal, cingulate, and parietal cortex appears to be critical for decision-making.

Functional magnetic resonance imaging (fMRI) studies with schizophrenia patients have shown that patients are unable to recruit a focal response even to a simple, automatic sequential finger movement task (Mattay et al 1997), even though there is no evidence of primary motor

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cortex dysfunction that would account for this result (Braus et al 2000). Both chronic and first-episode, never-medicated schizophrenia patients showed deficient working memory performance associated with an increased (Manoach et al 1999) or decreased activation (Barch et al 2001) or an increased spatial heterogeneity of dorsolateral prefrontal cortex activation (Manoach et al 2000). Reduced inferior frontal gyrus activation has been reported during a verbal working memory task in schizophrenia patients (Wexler et al 1998). Several investigators have proposed the notion of a task-dependent hypofrontality in schizophrenia patients (Curtis et al 1999; Volz et al 1999). Others have reported task-dependent increase in parietal activation (Callicott et al 1998). Some have suggested that schizophrenia patients are able to activate prefrontal structures under low-demand but not high-demand conditions (Fletcher et al 1998). These findings support the idea that schizophrenia patients may not exhibit a simple decrease of functioning of a circumscribed brain area but may show a task-dependent change of distributed activation across various brain regions.

Thus, if patients exhibit dysfunctional decision-making and show task-dependent dysfunctions in prefrontal cortex, which is one critical substrate for decision-making, then one would expect to find that schizophrenia patients show decreased prefrontal activation during decision-making. Four separate analyses were conducted to test different aspects of this hypothesis. First, to examine whether schizophrenia patients relative to comparison subjects show differences in activation during the two-choice prediction task, voxelwise activations were obtained in normal comparison subjects and schizophrenia patients. It was hypothesized that schizophrenia patients relative to comparison subjects show less prefrontal and parietal activation. Second, to determine whether schizophrenia patients showed activation differences in regions that showed task-related activation in both groups, a region of interest analysis was conducted across groups. It was hypothesized that schizophrenia patients show less task-related activation in right prefrontal and parietal regions of interest. Third, to link differences between task-related activations in schizophrenia patients and normal comparison subjects to response characteristics on the two-choice prediction task, a correlational analysis between behavioral characteristics during the two-choice prediction task and activation in different regions of interest was conducted. Fourth, to examine whether medication status significantly affected activation, the effect of no-treatment versus treatment with atypical antipsychotic medications on activation in regions of interest in schizophrenia patients was compared. It was hypothesized that treatment with antipsychotic medications significantly increases activation in prefrontal and parietal regions.

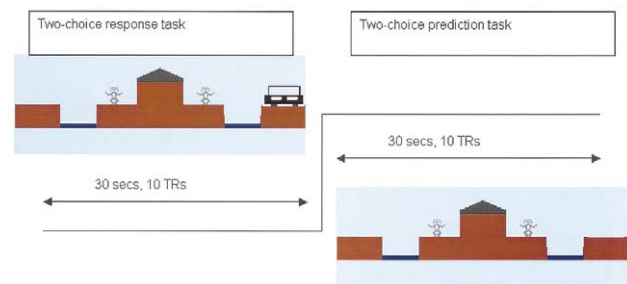


Figure 1. Functional magnetic resonance imaging block-design of the two-choice response task and the two-choice prediction task.

## Methods and Materials

### Subjects

The University of California, San Diego Institutional Review Board approved this study (#000730). Subjects included in the study, provided written informed consent for participation in the investigation. Initially seventeen schizophrenia patients and sixteen normal comparison subjects were enrolled into the study. Two schizophrenia patients and one normal comparison subject were excluded from subsequent analyses due to movement artifact in the echoplanar images. Thus, fifteen patients with the diagnosis of schizophrenia, continuous, according to the DSM-IV (American Psychiatric Association 1994), with an average age of 41.7 years  $\pm$  1.6 (range 30–53), an average education level of 14.4  $\pm$  .7 years (range 12–23), an average age of onset of 25.9 years  $\pm$  1.8 (range 18–39), and an average illness duration of 15.7 years  $\pm$  2.1 (range 7–34) participated in this study. The behavioral and functional neuroimaging data from these subjects was compared to a group of fifteen normal comparison subjects who were matched on age (mean 41.0  $\pm$  2.1, range 21–54) and education (mean 15.3  $\pm$  .56, range 12–21).

Diagnosis or diagnostic screening for all subjects was obtained by a structured clinical interview for DSM-IV diagnosis (SCID-P/NP) (Spitzer et al 1992). Subjects with a major depressive disorder, bipolar, posttraumatic stress, panic, or obsessive-compulsive disorder were excluded from the study. Subjects with nonremovable materials that respond to high magnetic fields (e.g., metal fragments) were also excluded. At the time of testing the schizophrenia patients were clinically stable; seven patients were treated with atypical antipsychotic medication, two patients were treated with typical antipsychotic medications, and six patients were not treated with any antipsychotic medications at time of testing.

### Task

The two-choice prediction task has been described in detail elsewhere (Paulus 1997). Briefly, a house with a person to the left and right is shown on a computer screen (Figure 1). The goal for the subject is to respond in such a way that the person on the left or right side can meet up with a car that is presented on the far left or right side of the screen. For the *two-choice prediction task*, the subject is told to decide on which side the car will be presented. AFTER the subject has made a response, the car is

presented for 300 msec on the far left or right side. If the selected response matches the side where the car is presented, the person of the selected side meets up with the car. Unbeknownst to the subject, the car is presented according to a predetermined schedule, which utilizes the response of the subject to assure that 50% of the responses will be "correct" predictions. For the *two-choice response task*, the car is presented on the left or right side BEFORE the subject is asked to respond. The duration of each trial depends on the latency to make a decision, i.e., the time between presentation of the initial situation and the selection of the response. Therefore, the number of trials per experimental block depends on the subjects average decision-time during the block. The key difference between these two tasks is that during the *two-choice prediction task*, the *subject does not know the correct response in advance*, has to decide in the presence of uncertainty, and can use the previous responses, stimuli, and outcomes to determine the current response. In comparison, during the *two-choice response task* the *subject knows the correct answer before selecting a response*, decides in the presence of certainty, and does not need to use the sequences of previous responses, stimuli, or outcomes.

### Behavioral Measures

The following variables were obtained during each block: 1) the response selected by the subject (*left or right*); 2) the computer-selected presentation of the stimulus (*left or right*); and 3) the latency to select a response (time from the presentation of the current situation to button press). Based on these variables, the strategies of decision-making in the presence of uncertainty were assessed by two sets of measures: 1) general response biases: the number of *left* versus *right* responses or *stay* (a *left* response followed by *left* response) versus *switch* responses (*left* followed by *right* response); 2) mutual information measures (logarithmic likelihood ratio between the observed and the expected frequencies of an event [Herzel and Grosse 1997]) are used to quantify the degree to which the current response is determined by the previous response, the previous stimulus, or a combination of both. For example, if two responses are equally likely (1 bit of information) and are completely predicted by the previous response, then the mutual information measure between the previous response and the current response is 1 bit.

### fMRI Protocol and Image Analysis Pathway

Magnetic resonance images were obtained using a 1.5 Tesla whole-body system (Siemens, Erlangen, Germany). Anatomical T1-weighted images of the whole brain (MPRAGE, repetition time [TR] = 11.4 msec, echo time [TE] = 4.4 msec, flip angle = 10°, field of view [FOV] = 256 × 256, 1-mm pixels, 1-mm slice thickness) were obtained sagittally to identify the anterior/posterior commissure, to co-register the functional image, and to transform the images into Talairach space (Talairach and Tournoux 1988). Thirty-two slices of T2\*-weighted images were obtained in the transverse plane using gradient-recalled echo planar imaging (TE = 40 msec, flip angle = 90°, 64 × 64 pixel FOV = 220 × 220 mm, 3-mm slice thickness) every 3000 msec for 112 repetitions, yielding a voxel size of 3.43 mm × 3.43

mm × 3 mm to minimize signal dropout related to magnetic susceptibility variations in the orbitofrontal cortex. The task was presented to the subjects using an LCD projector, back-projected onto a screen at the subjects' feet, which could be seen via a mirror attached to the head coil. Subjects requiring corrective lenses were provided with a pair of plastic-framed lenses that approximated their degree of correction. Motor responses were made using a fiber-optic button box. The two-choice prediction task ("on" condition) and the two-choice response task ("off" condition) were presented in an "off-on" repeated block design. Each block lasted 30 sec or 10 TRs. The entire experiment lasted 11 alternating "off-on" blocks, starting and ending with an "off" condition.

All subsequent image processing was done using the Analysis of Functional Neuroimages (AFNI) software package (Cox 1996). Echoplanar images were co-registered using a three-dimensional-coregistration algorithm to the echoplanar image that resulted in the smallest amount of image translation and rotation relative to all other images. Echoplanar images of each subject were inspected for residual movement artifacts. For each voxel, signal intensity across the 112 repetitions of the T2\*-weighted images was regressed onto a reference vector that coded the experimental condition. The resulting fit coefficient, which quantifies the change of the echo-planar signal intensity across task conditions, was used as the key variable to measure voxelwise activation (Cohen 1997). A Gaussian filter with FWHM 3.4 mm was applied to the fit-coefficient image to account for individual variations of the anatomical landmarks. The regression coefficient images of each subject were normalized to Talairach coordinates.

Four separate analyses were conducted. First, a voxelwise mixed-model (fixed effect: task-type; random effect: subjects) analysis of variance (ANOVA) was computed using the program 3dAnova2 of the AFNI software package, which was followed by volume-thresholding (volume 350  $\mu$ L, connectivity radius = 3.43 mm) to correct for multiple comparisons, to yield a corrected clusterwise  $p < .05$  (Forman et al 1995). Clusters of the ANOVA main effect, group effects, and group-by-task interactions were used to define regions of interest for post hoc comparisons across groups. Second, for each subject the average fit coefficient was obtained based on the region of interest from the first analysis. Independent  $t$  tests were used to compare the average fit coefficients across groups. Third, the AFNI program 3dregana was used to compute a regression coefficient between the behavioral measures obtained during fMRI scanning from the two-choice prediction task and the fit coefficient quantifying the changes in echoplanar signal intensity. Fourth, the average fit coefficients obtained from the regions of interest were used as dependent measures in a one-way (medication status) ANOVA followed by regionwise post-hoc comparisons. Fifth, medication status was entered as an independent variable in a one-way ANOVA to determine whether the average activation in functional regions of interest differed across unmedicated schizophrenia patients versus those treated with typical or atypical antipsychotics.

### Statistical Analysis

A mixed-model ANOVA (i.e., one random between-subjects factor [schizophrenia patients vs. normal comparison subjects]

Table 1. Behavioral Responses during the Two-Choice Response and Prediction Task

Measure	Two-choice response task				Two-choice prediction task				Statistics	
	Comparison subjects		Schizophrenia patients		Comparison subjects		Schizophrenia patients			
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	<i>F</i> (1,28)	<i>p</i>
Responses/block	32.413	1.724	30.24	1.724	30.627	2.305	28.68	2.305	.01	ns
P (right response)	.506	.007	.509	.007	.503	.016	.501	.016	.34	ns
P (switch response)	.494	.015	.513	.015	.448	.028	.463	.028	.01	ns
Mutual information	.029	.011	.047	.011	.053	.020	.067	.020	.020	ns
Win-stay mutual information	.018	.006	.043	.006	.092	.039	.280	.039	9.230	<.01

P, probability.

and two fixed within-subjects factors [block: two-choice prediction task or two-choice response task; repetition: 5 repetitions of the block]) was used to determine whether the behavior measures differed across groups and across the two task conditions. The effect of block tests for behavioral differences across task conditions and the effect of repetition tests for change in the behavior during the fMRI session. To adjust the degrees of freedom for the nonparallel correlations among measures between groups (violations of sphericity), Greenhouse-Geisser (GG) corrections were applied.

## Results

### Behavioral Measures

As shown in Table 1, schizophrenia patients did not differ from comparison subjects on the number of responses made during a trial block, the probability of selecting the RIGHT response, the probability of switching from LEFT to RIGHT or RIGHT to LEFT, or the degree to which the previous response predicted the current response. The responses of schizophrenia patients relative to those of comparison subjects were more predictable by a win-stay/lose-shift strategy as measured by the win-stay/lose-shift mutual information. As shown in Figure 2, schizophrenia patients made 70% win-stay consistent responses (comparison subjects 65%) and 70% lose-shift consistent responses (comparison subjects 55%). Thus, although there was no difference in basic response bias or other performance measures, in contrast to previous studies, the selection of responses generated by schizophrenia patients were more influenced by the previous outcome.

### fMRI Measures

The mixed-model ANOVA revealed a task effect common to both groups in three main areas. First, right premotor (Brodmann's area [BA] 6), dorsolateral prefrontal (BA 9), insula (BA 13), and inferior prefrontal cortex (BA 47) showed increased activation during the two-choice prediction task relative to the two-choice response task in both schizophrenia patients and comparison subjects (Figures 3

and 4, Table 2). Second, bilateral precuneus (BA 7) and right inferior parietal lobule (BA 40) were significantly more active during the two-choice prediction task in both groups. Third, medial prefrontal cortex (BA 10) and subgenual anterior cingulate (BA 32) were significantly more active during the two-choice response task relative to the two-choice prediction task (Figures 3 and 4). Thus, a network of fronto-parietal cortex showed significant task-related activation during decision-making in the presence of an uncertain outcome in both groups.

A task-by-group interaction effect was found in six areas (Table 2). These interactions were due to a difference in activation patterns across task conditions in the schizophrenia group relative to the normal comparison group and comprised two types of interactions. First, in contrast to normal comparison subjects, schizophrenia patients showed less activation during the two-choice prediction relative to the two-choice response task in the left inferior frontal gyrus (BA 44), medial frontal gyrus (BA 6,8), and right superior temporal gyrus (BA 33).

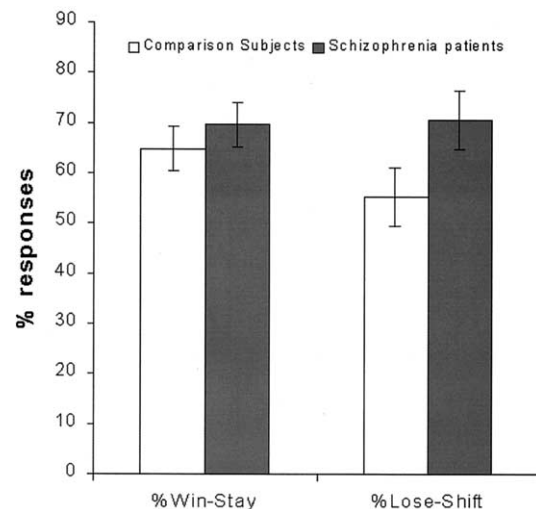


Figure 2. Schizophrenia patients selected more lose-shift consistent responses than normal comparison subjects.

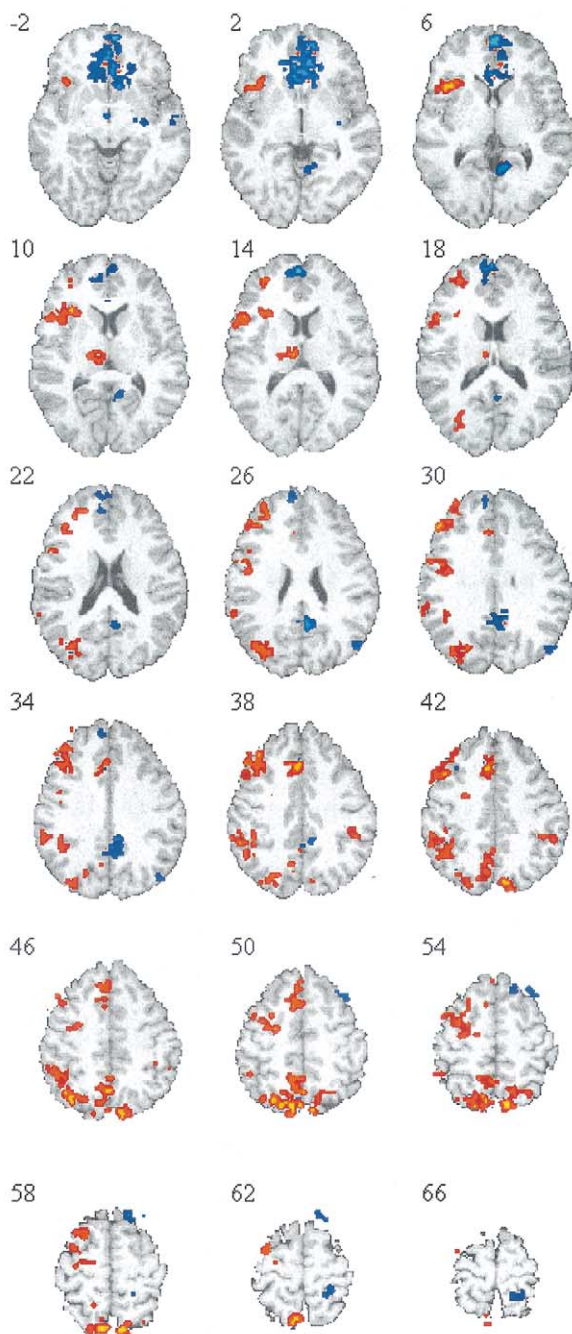


Figure 3. Volume-thresholded task effect in both groups. Red: two-choice prediction task > two-choice response task; blue: two-choice response task > two-choice prediction task. Numbers indicate z-coordinate of the axial slice.

Second, schizophrenia patients showed more activation during the two-choice prediction task relative to the two-choice response task in the left inferior parietal lobule (BA 40) and the left postcentral gyrus (BA 2) (Figures 5 and 6). In three out of the six regions, the average activation in these areas predicted the frequency of win-

stay but not lose-shift consistent responses in schizophrenia patients as well as in normal comparison subjects (data not shown). Specifically, a larger activation in medial prefrontal cortex [ $F(1,14) = 89.96, R^2 = .86$ ], postcentral gyrus [ $F(1,14) = 21.59, R^2 = .59$ ], and inferior parietal lobule [ $F(1,14) = 33.12, R^2 = .69$ ] during the two-choice prediction task predicted a higher frequency of win-stay consistent responses (Figure 6). Therefore, the interaction effect was related in part to a decision-making strategy that differed across these groups.

The medication status (no current medication, typical antipsychotic medication, atypical antipsychotic medication) of schizophrenia patients significantly influenced two key areas that showed task-related increase in activation during the two-choice prediction task. Schizophrenia patients that were currently treated with atypical antipsychotic medications ( $n = 7$ ) showed significantly more task-related activation in right middle frontal gyrus [BA 9,  $F(2,14) = 5.730, p < .05, \text{LSD } p < .01$ ] and precuneus [BA 7,  $F(2,14) = 3.31, p = .06, \text{LSD } p < .01$ ] (Figure 7). In comparison, neither age [ $F(2,14) = 0.722, \text{ns}$ ], education [ $F(2,14) = 2.38, \text{NS}$ ], or illness duration [ $F(2,14) = 0.352, \text{ns}$ ] differed across the treatment groups. Thus, schizophrenia patients treated with atypical antipsychotic medications showed task-related activation in both prefrontal and parietal cortex that was more similar to that of comparison subjects.

## Discussion

This study yielded five main results. First, schizophrenia patients showed more outcome-dependent response selection than comparison subjects. Second, relative to comparison subjects schizophrenia patients showed similar levels of task-related activation in the right prefrontal cortex but less activation in the parietal cortex. Third, in contrast to comparison subjects, schizophrenia patients showed less task-related activation in right inferior prefrontal, medial prefrontal, and right superior temporal gyrus but more task-related activation in the postcentral gyrus and left inferior parietal lobule. Fourth, in three of the six regions that showed a task-by-group interaction, more task-related activation was predictive of an increased frequency of win-stay consistent responses. Fifth, task-related activation in both right prefrontal and bilateral parietal cortex was significantly higher in medicated compared to unmedicated schizophrenia patients. Taken together, these results support the hypothesis of a prefrontal-parietal cortex dysfunction during decision-making in schizophrenia patients, which is associated with an increase in outcome-dependent response selection.

In contrast to our first hypothesis, schizophrenia patients did not show significantly less dorsolateral prefrontal

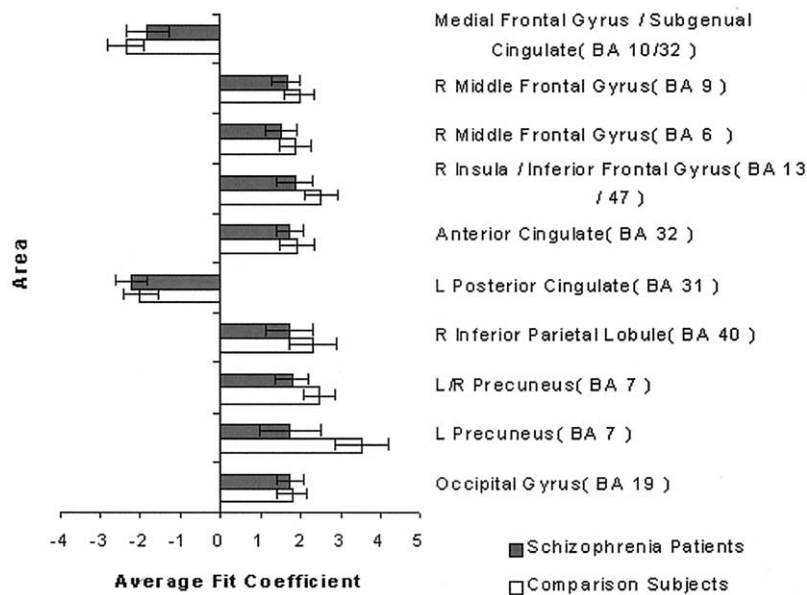


Figure 4. Average fit coefficient and standard errors for functional regions of interest obtained from the task-effect of the mixed analysis of variance. BA, Brodmann's area; R, right; L, left.

tal task-related activation. There have been several fMRI studies with schizophrenia patients that have shown conflicting results related to task-related prefrontal activation. In working memory tasks, schizophrenia patients showed deficient performance associated with an increased activation (Manoach et al 1999) or an increased spatial heterogeneity of dorsolateral prefrontal cortex activation (Manoach et al 2000). In contrast, others have shown a selectively reduced activation in left dorsolateral prefrontal cortex in never-medicated, first-episode schizophrenia patients (Barch et al 2001).

Several investigators have proposed the notion of a task-dependent hypofrontality in schizophrenia patients (Curtis et al 1999; Volz et al 1999). It has been suggested that schizophrenia patients are able to activate prefrontal structures under low-demand but not high-demand conditions (Fletcher et al 1998). In this study, two factors may have contributed to the similar levels of activation in the right dorsolateral prefrontal cortex. First, 9 of the 15 patients were medicated at time of testing. As shown in Figure 7, medicated patients showed significantly greater task-related activation in both right prefrontal and bilateral parietal cortex. Thus, medication effects may have contributed to the lack of activation difference between schizophrenia patients and normal comparison subjects in the prefrontal cortex. This finding is consistent with a recent report of an increase in both prefrontal and parietal activation in a working-memory task after switching schizophrenia patients to risperidone (Honey et al 1999). Second, the two-choice prediction task is a complex decision-making paradigm that includes inhibitory, working-memory, response sequencing, and local context demands. These multiple processing demands may facilitate

the activation of the prefrontal cortex and thus attenuate differences between schizophrenia patients and comparison subjects. This hypothesis can be tested by parsing different components of decision making and examining these components separately in schizophrenia patients versus normal comparison subjects.

Consistent with the first and second hypothesis, in contrast to normal comparison subjects, schizophrenia patients showed attenuated task-related activation in the left precuneus (BA 7). This finding is consistent with a disruption of a spatial attentional network. Specifically, transmodal centers of higher association areas, which include parietal, prefrontal, and cingulate areas may provide the key substrate for attentional, motivational, and emotional modulations of sensorimotor data (Mesulam 1998). The attenuated activation of the precuneus supports the hypothesis of disrupted spatial processing (Mesulam 1999). In the two-choice prediction task, subjects frequently report monitoring the left and right side of the computer screen for signs predicting the car. These subjective reports will require follow-up investigations using eye-tracking during this decision-making task. The increase in inferior parietal lobule activation may be due to increased error-related monitoring in schizophrenia patients during the two-choice prediction task. This notion is consistent with the behavioral results that show that increased activation in the inferior parietal lobule, an area that showed more task-related activation in schizophrenia patients relative to normal comparison subjects, was associated with an increase in win-stay consistent responses.

The increased frequency of a win-stay/lose-shift strategy during the two-choice prediction task in schizophrenia patients differs from previous behavioral results outside

Table 2. Volume-Thresholded Clusters of the Average Fit Coefficient (AFC) and its Standard Error (SEM) in Talairarch Coordinates (x,y,z) of Task-Related Activation and Task-by-Group Interaction

	Volume ( $\mu$ L)	x	y	z	AFC	SEM (AFC)	R/L	Description	BA
Task effect	675	-3	54	3	-3.0805	.1743	L	Medial frontal gyrus	10
	378	35	42	50	-1.283	.0582	R	Middle frontal gyrus	8
	351	-32	20	49	-1.7711	.0882	L	Superior frontal gyrus	8
	2619	39	25	33	1.8198	.0364	R	Middle frontal gyrus	9
	999	5	51	14	-2.3443	.1086	R	Medial frontal gyrus	9
	540	24	42	33	1.9366	.1108	R	Middle frontal gyrus	9
	486	28	46	16	1.8687	.0845	R	Superior frontal gyrus	10
	405	30	44	25	1.885	.1214	R	Middle frontal gyrus	10
	459	-23	66	-20	-2.5221	.3122	L	Superior frontal gyrus	11
	540	47	13	14	1.8294	.0768	R	Inferior frontal gyrus	45
	405	65	34	27	-1.0601	.0579	R	Middle frontal gyrus	46
	513	-33	23	-22	-2.5788	.1138	L	Inferior frontal gyrus	47
	4320	0	36	-2	-2.1753	.0434	R	Anterior cingulate	32
	1971	5	19	42	1.8095	.0567	R	Cingulate gyrus	32
	540	-1	31	-10	-2.659	.1251	L	Anterior cingulate	32
	378	39	-85	11	-1.5236	.0964	R	Middle occipital gyrus	18
	594	-19	-40	64	-1.9886	.0847	L	Superior parietal lobule	5
	4536	8	-64	47	2.1047	.0447	R	Precuneus	7
	1620	-12	-72	50	2.4972	.0986	L	Precuneus	7
	2457	30	-72	33	1.8561	.0528	R	Occipital gyrus	19
	1458	-5	-48	29	-2.018	.0677	L	Posterior cingulate	31
	945	44	-47	41	1.8486	.0626	R	Inferior parietal lobule	40
	432	54	-38	34	1.6045	.0581	R	Inferior parietal lobule	40
	432	40	-44	33	1.5285	.0686	R	Supramarginal gyrus	40
	1539	34	18	5	2.0079	.071	R	Insula	13
	702	9	-17	11	1.5527	.0951	R	Thalamus	
	810	-52	-11	-10	-1.6671	.0661	L	Middle temporal gyrus	21
	351	47	-46	-11	1.6859	.089	R	Fusiform gyrus	37
	1107	-53	-73	26	-1.418	.0536	L	Middle temporal gyrus	39
	Task-by-group interaction	405	-46	45	0	-3.5597	.1906	L	Inferior frontal gyrus
567		-11	-24	62	-3.1092	.1448	L	Medial frontal gyrus	6
351		2	42	43	-4.2557	.2911	R	Medial frontal gyrus	8
567		-51	-30	54	3.7968	.1851	L	Postcentral gyrus	2
405		-50	-38	32	2.8905	.1389	L	Inferior parietal lobule	40
	351	-26	9	-25	-5.4748	.3248	L	Superior temporal gyrus	33

R, right; L, left; BA, Brodmann's area.

the fMRI scanner (Paulus et al 1999). This strategy relies on two pieces of information. First, "was the stimulus presented previously on the left or right side?" (keeping information online) and second, "was the previous prediction correct or incorrect?" (response reinforcement). This strategy as any other strategy, however, does not increase the number of correct predictions during the two-choice prediction task. The current finding may have resulted from the combination of the experimental design and the differences in the neural activation found in schizophrenia patients. First, for the functional neuroimaging study the subjects were presented with alternating blocks of the choice prediction and the choice response task. The key feature of the two-choice response task is to detect the location of the stimulus and to generate an appropriate response. Thus, in contrast to the two-choice prediction task, the stimulus during the two-choice response task is a cue for appropriate responding; however, if the previous

instructional set is maintained ("respond to the location of the stimulus"), the subject may respond to where the stimulus has been presented on the previous trial, which can increase the frequency of win-stay/lose-shift consistent responses. Second, in normal comparison subjects, a lower frequency of win-stay/lose shift responses was correlated with an increased activity in the precuneus (Paulus et al 2001a), a structure that is critical for response-reinforcement relationships (Platt and Glimcher 1999). In this study schizophrenia patients showed reduced activity changes in the precuneus (left BA 7) relative to comparison subjects and an increase in the left inferior parietal lobule. Therefore, the increase in win-stay/lose-shift consistent responses may also be due to parietal activation differences in schizophrenia patients. The increased frequency of win-stay/lose-shift may be due to an increased perseveration of the previous instructional set and a reduced sensitivity to response reinforcement.

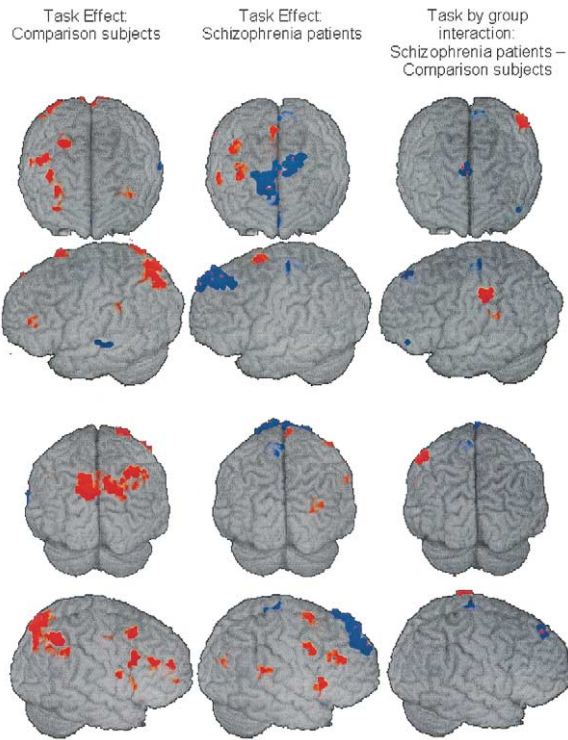


Figure 5. Volume-thresholded task-related activation for normal comparison subjects and schizophrenia patients.

Both hypotheses can be examined by using an experimental set-up with a randomized block design and by testing the response characteristics during different levels of reinforcement, respectively.

The task-by-group interaction in the medial prefrontal

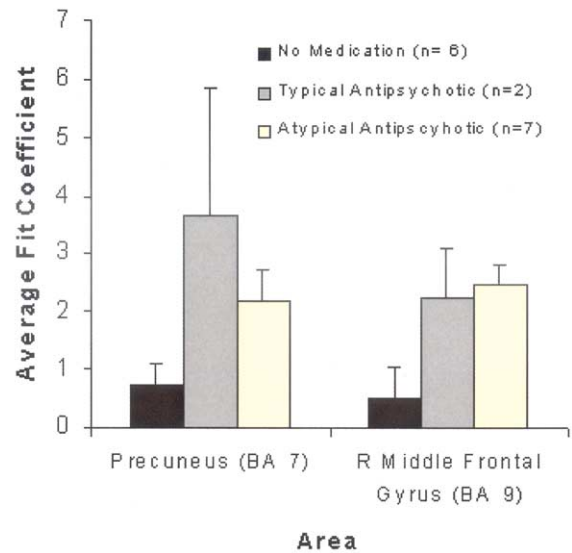


Figure 7. Medication effect on task-related activation in precuneus and right middle frontal gyrus. BA, Brodmann's area; R, right.

cortex (BA 6,8) further supports the notion that schizophrenia patients may not establish an outcome-independent rule to govern response selection. Specifically, this area has been implicated in processing a sequence of actions (Crozier et al 1999) and contextual monitoring (Henson et al 1999). In addition, the activation of medial prefrontal cortex has been related to the monitoring of sequences for predictable events (Koechlin et al 1999). Similarly, task-related activation in the left inferior pari-

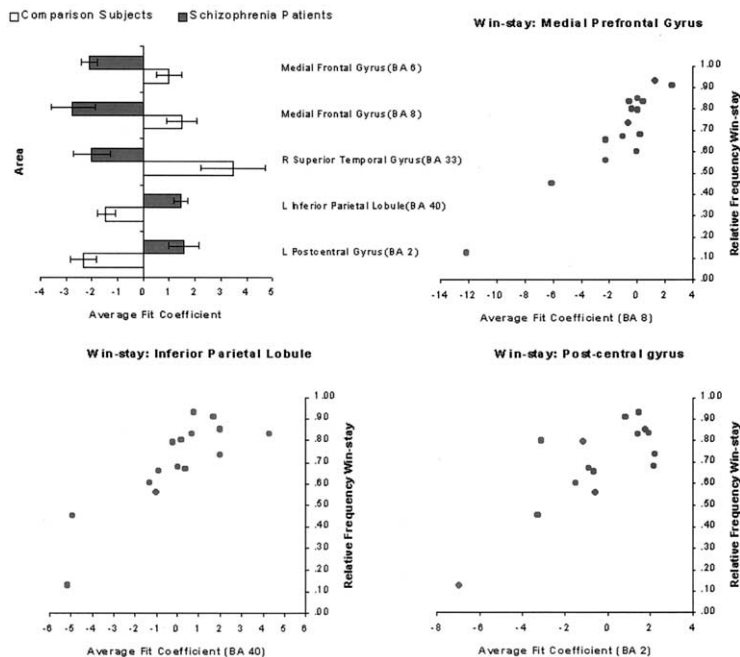


Figure 6. Average fit coefficient and standard error of regions that showed a task-by-group interaction, and relationship between region-specific fit coefficient and win-stay consistent responses in three regions of interest. BA, Brodmann's area; R, right; L, left.

etal lobule in schizophrenia patients, which was not observed in normal comparison subjects, may be due to an increase in perceived sequence complexity (Sadato et al 1996). The combination of the behavioral findings (i.e., an increase in win-stay/lose-shift consistent responses in schizophrenia patients) and the correlational evidence (i.e., a positive correlation between degree of activation and win-stay consistent responses in three of the six areas in which schizophrenia patients showed a different activation pattern than normal comparison subjects) supports the general hypothesis that schizophrenia patients monitored the sequences of stimuli but did not utilize this sequence to form an outcome-independent response strategy.

In support of the fourth hypothesis and consistent with previous fMRI findings (Honey et al 1999), medication status significantly affected task-related activation. Specifically, schizophrenia patients that were treated with either typical or atypical antipsychotic medications showed more task-related activation of the right middle frontal gyrus (BA 9) and precuneus (BA 7). Although medication status was not controlled prospectively, corollary analyses show that neither age, education, nor illness duration differed across groups. In addition, these variables did not correlate with activation in the functional regions of interest. Future studies will need to examine prospectively whether treatment with antipsychotic medications improves task-related activation in prefrontal or parietal cortex and whether this increase is related to the generation of different response strategies on this simple decision-making task.

This investigation has several limitations. First, the behavioral process underlying the increased frequency of win-stay/lose-shift responses during the two-choice prediction task in schizophrenia patients may be due to the experimental design. Second, the neuroimaging results are based on a relatively small sample of subjects. Future studies will need to be conducted to replicate this finding. Third, medication status was not controlled for in this study (i.e., schizophrenia patients were on typical, atypical, or no medication). Fourth, the fMRI group analyses were conducted in Talairach space, i.e., the functional images were transformed into a standard coordinate system. It is well known that schizophrenia patients show significant structural alterations relative to normal comparison subjects, which may differentially affect the transformation. Therefore, future studies will need to replicate this finding using both standard Talairach space and a region of interest analysis pathway in untransformed images.

Despite these limitations, schizophrenia patients exhibit response sequences during the two-choice prediction task that are consistent with an outcome-perseverative strategy when presented with alternating tasks that require decision making in the presence of uncertainty and stimulus match-

ing. Most importantly, this decision-making dysfunction is associated with less activation of the medial prefrontal cortex and an increased activation in the parietal cortex, which points toward a fronto-parietal dysregulation as the putative neural substrate dysfunction underlying the fundamental dysregulation of decision making in schizophrenia patients.

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