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Procedural learning in schizophrenia investigated with functional magnetic resonance imaging

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Abstract

A cerebral basis for the acquisition and retention of procedural knowledge in schizophrenia was examined with 1.5 T functional MRI during an embedded sequence Serial Reaction Time Task (SRTT) in 10 chronic medicated patients and 15 healthy controls. Comparable procedural learning was observed in both groups, suggesting that the impairment reported in previous schizophrenia samples may not be robust. Consistent with previous fMRI reports, procedural learning in the control group was associated with activity in the dorsal striatum, anterior cingulate, parietal cortex and frontal cortex. Greater procedural learning related activity was observed in the control relative to the schizophrenia group in the bilateral frontal, left parietal and bilateral caudate regions. Patients did not activate frontal or parietal areas while responding to the embedded sequence within the SRTT, but greater activation during procedural learning was observed relative to the control sample in the right anterior cingulate, left globus pallidus and the right superior temporal gyrus. Thus, despite comparable instantiation of procedural learning in schizophrenia, the cerebral activation associated with this cognitive skill was abnormal. The paucity of activity in bilateral frontal cortex, left parietal cortex and bilateral caudate nucleus may represent cerebral dysfunction associated with schizophrenia, whereas the hyperactivation of the right superior temporal gyrus, the right anterior cingulate cortex and the left globus pallidus may represent a compensatory cerebral action capable of facilitating near-normal task performance. The results are thus consistent with a neurodevelopmental pathology impinging on fronto-subcortical circuitry.

Keywords: Neuroscience; Neuropsychology; Schizophrenia; Cognition; Memory; Procedural learning; Serial response time; fMRI; Subcortical

1. Introduction

Procedural learning refers to the ability to acquire a motor skill or cognitive routine in the absence of declarative knowledge (Cohen and Squire, 1980). Measures of procedural learning, such as the embedded sequence Serial Reaction Time Task (SRTT), are sensitive to the differentiation between subcortical and cortical processing networks. The SRTT provides a measure of reaction time to a rhythmic pattern of sequenced stimuli intermittently repeated within a random order of similar stimuli. In the absence of conscious awareness of the sequence, procedural learning is demonstrated by faster response times on sequenced relative to random blocks of trials. Applications of the embedded series SRTT have consistently dissociated implicit memory systems presumed reliant on frontal and

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subcortical structures from explicit memory systems presumed reliant on medial temporal lobe structures. For example, SRTT procedural learning is relatively spared, despite the marked impairment of explicit memory in temporal lobe degenerative dementias such as Alzheimer's disease (Knopman and Nissen, 1987) or amnestic disorders (Nissen et al., 1989). In contrast, despite relatively spared explicit memory, SRTT deficits have been associated with dorsal striatum dysfunction from subcortical lesions, Huntington's disease and Parkinson's disease (Gomez Beldarrain et al., 1998, 1999, 2002; Knopman and Nissen, 1991; Pascual-Leone et al., 1993). Neuroimaging studies have confirmed the importance of subcortical structures to SRTT performance as well, most notably in PET and fMRI demonstrations of task-specific activations in the caudate, putamen, globus pallidum, superior and the inferior frontal cortex, anterior cingulate, inferior parietal lobe and cerebellum (Daselaar et al., 2003; Kumari et al., 2002; Martis et al., 2004; Rauch et al., 1997a,b, 2001; Schendan et al., 2003; Thomas et al., 2004; Willingham et al., 2002).

Schizophrenia results in a significant reduction of functional status secondary to a wide spectrum of cognitive deficits likely related to early cerebral dysfunction (Harvey et al., 2004). Post-mortem and in vivo neuroimaging investigations have repeatedly implicated the prefrontal cortex, dorsal striatum and, to a lesser extent, the cerebellum, in this neuropathology (Shenton et al., 2001). Models have been proposed to assimilate the heterogeneous neuropathology with key clinical symptoms and cognitive impairments in schizophrenia by postulating a central deficit within cortical-striatal or cortico-cerebellum-thalamo-cortical (CCTC) circuits (Andreasen et al., 1999; Buchsbaum, 1990; Buchsbaum et al., 1999). Dysfunction in the cortical or subcortical components of these circuits would be supported by impairment of procedural learning, but several measures of procedural learning appear intact in schizophrenia (Altshuler et al., 2004; Purdon et al., 2003; Takano et al., 2002; Clare et al., 1993). A few studies have reported procedural learning impairment, but the deficits may reflect potent D2 receptor antagonism in the dorsal striatum from typical antipsychotic medications (Kumari et al., 1997; Purdon et al., 2002, 2003; Bedard et al., 1996, 2000; Peretti et al., 1997; Scherer et al., 2004; Danion et al., 1992; Schwartz et al., 1996). This ambiguity extends to the SRTT in reports of mild (Green et al., 1997) and more substantial (Kumari et al., 2002) impairments in medicated patients, a discrepancy reported between impaired procedural learning in patients treated with typical but not atypical neuroleptics (Stevens et al., 2002), and a procedural learning impairment limited to the acute phase of the illness (Exner et al., 2006). The only prior fMRI study of SRTT performance in schizophrenia reported activation deficits in the frontal cortex, striatum, thalamus and cerebellum relative to a control sample (Kumari et al., 2002). However, the pathognomonic relevance of this observation to fronto-striatal or CCTC circuit dysfunction is undermined by the possible attribution of the SRTT performance deficit to the typical neuroleptic treatment received by the schizophrenia patients, or perhaps to a feature of the experimental design that exposed the control group to more embedded sequences than the schizophrenia group, a potential limitation that may have been compounded by the use of a novel SRT task with much greater spatial processing demands.

The current study addressed the potential confounding effects from typical antipsychotic medications and deficient exposure to stimuli which have undermined a confident attribution of SRTT procedural learning deficits in schizophrenia to a disease-specific cerebral dysfunction in cortico-striatal or CCTC circuits (Andreasen et al., 1999; Buchsbaum et al., 1999; Buchsbaum, 1990). A modification of the experimental design applied in the prior fMRI examination during SRTT procedural learning was developed to provide a less encumbered test of the cortical–subcortical pathology models for schizophrenia. In the current application, a sample of patients with chronic schizophrenia treated predominantly with atypical neuroleptics, and a matched control group, underwent fMRI while completing an embedded series SRTT that ensured equivalent exposure to the embedded series in both groups.

2. Methods

2.1. Subjects

Thirteen right-handed outpatients with schizophrenia and 15 right-handed healthy controls were recruited, but MRI data from three patients were unusable due to excessive head movement artifact. Demographic and clinical characteristics are summarized in Table 1. Groups were matched for age and gender, but the control sample had more education, $t(23)=3.23$, $p=0.004$. The diagnosis of schizophrenia was confirmed with the SCID-IV TR (First et al., 1997). The severity of psychosis was quantified with a Global Assessment of Function (GAF) (First et al., 1997), and with the Positive and Negative Syndrome Scale (PANSS) which provides subscale scores corresponding to positive symptoms (e.g. hallucinations, delusions, conceptual disorganization), negative symptoms (e.g.

Table 1
Demographic and clinical characteristics of participants

	Schizophrenia (N=10)		Controls (N=15)	
Male	N	%	N	%
	8	80	10	67
	Mean	S.D.	Mean	S.D.
Age (years)	33.5	7.5	31.3	11.2
Education (years)	13.4	2.2	17.8	3.9
Illness duration (years)	11.5	6.7		
PANSS [a]				
Positive	14.7	3.7		
Negative	10.7	2.4		
General	26.1	4.2		
GAF [b]	50.6	15.9	90.9	5.5

[a] Positive and Negative Syndrome Scale.
[b] Global Assessment of Functioning.

blunt affect, emotional withdrawal, speech spontaneity) and general psychopathology (e.g. anxiety, depression, poor impulse control) (Kay et al., 1987). The patients had been on a stable medication regime for at least two months that included atypical antipsychotic drugs alone (n=6; clozapine 100, 400 and 450 mg/day; risperidone 4 mg; quetiapine 400 mg; quetiapine 50 mg; and clozapine 425 mg), combinations of atypical and typical antipsychotic drugs (n=3; fluanxol decanoate 50 mg per 2 weeks and quetiapine 225 mg/day; zuclopenthixol decanoate 150 mg per 2 weeks and olanzapine 5 mg; zuclopenthixol decanoate 175 mg per 4 weeks and quetiapine 200 mg). One patient was also receiving 2 mg of benztropine mesylate.

Healthy controls were free from current or prior Axis I psychiatric disorders or a family history of schizophrenia. Participants were excluded if they reported a history of head injury or neurological disease, systemic medical disease, or current alcohol or substance abuse or prior dependence. The study was approved by the Health Research Ethics Review Board of the University of Alberta and all subjects provided written informed consent to participate.

2.2. Serial Reaction Time Test

During scanning, subjects performed an embedded sequence Serial Reaction Time Task (SRTT) consisting of an asterisk that alternated between four boxes arranged horizontally on a computer screen (Rauch et al., 1997a,b). Subjects were instructed to quickly and accurately identify the target location by pressing a corresponding response key. The left two stimuli locations corresponded to left middle and index fingers, and the right locations corresponded to the right index and middle fingers. On each trial, stimuli appeared for 800 ms prior to a 200 ms inter-trial interval. Sixty trials comprised one sequenced or one random block. Within sequenced blocks, anticipated to elicit procedural learning, the location of the asterisk was determined by a 12-element second order conditional (SOC) sequence of trials repeated five times. Subjects were not informed of the sequence. Random blocks were included to allow a reaction time (RT) benchmark after correcting for practice-related improvements in simple motor speed. The locations for the stimuli were pseudorandomly assigned with the constraints that all four locations appeared with equal frequency within a block, and no location was repeated consecutively. Subjects completed two fMRI scanning runs, each consisting of three sequenced and three random blocks that alternated in a blocked AB manner, with each block separated by an 18 s fixation point resting period. Prior to entering the MRI scanner, subjects completed 5 consecutive blocks of 72 sequenced trials on a computer keyboard.

Separate analyses were undertaken for prescan and scanned blocks of trials. Incorrect trials were excluded to avoid outliers from errors or timed out responses. Very accurate discriminations produced excessive negative skew in both groups, necessitating nonparametric analysis of accuracy rates for comparisons between groups (Wilcoxin U) and within groups (Friedman's chi-square). The median reaction time for correct trials within each of the prescan blocks was subjected to a 5 (block) by 2 (group) analysis of variance with block as a within subjects variable and group as a between subjects variable, followed by a between groups comparison of the difference in median reaction times between blocks 1 and 5. The median reaction time for correct trials within each of the fMRI scanned blocks was subjected to a 6 (block) by 2 (condition: sequenced vs random) by 2 (group) analysis of variance with block and condition as full factorial within subjects variables, followed by a between groups comparison of the difference in median reaction times on sequenced versus random blocks of trials.

2.3. Imaging acquisition and analysis

All structural and functional MRI images were acquired during one session on a Seimens Sonata 1.5 T scanner. Twenty-five contiguous axial 4 mm thick functional images were acquired parallel to the AC-PC line using a T2*EPI sequence (matrix = 128 × 128, voxel size 1.72 × 1.72 × 4 mm, TR = 3000 ms). Each of the two runs

produced 156 volumes after exclusion of the first three volumes. A high resolution, 144 slice, 1×1×1 mm voxel size 3D structural image was also acquired using an MPRAGE sequence.

Processing of images and statistical analyses were carried out using Brainvoyager QX software (Brain Innovation, Maastricht, The Netherlands) except where noted. Motion correction, slice scan timing correction, spatial smoothing (8 mm FWHM), linear and non-linear temporal signal drift removal were applied to the raw fMRI images prior to statistical analysis. Functional images for each subject were co-registered to their respective structural image by applying scanner positioning header data to grossly align the images, and then applying a multi-scale intensity adjustment to fine-tune the alignment. After co-registration, the structural and functional images were warped into standard Talairach space (Talairach and Tournoux, 1988) and functional data were interpolated to a 3×3×3 mm voxel size. A priori delineation of voxels-of-interest for analysis by creation of Brainvoyager™ masks diminished the risk of Type I error (Goebel et al., 1998), with one mask created for the cortex and a second mask created for the subcortical region spanning the thalamus, caudate and putamen.

Statistical analysis of fMRI data proceeded by modeling each subject's functional time course data at each voxel using a boxcar function with sequenced and random blocks entered as predictors and convulved with a gamma function to account for the time-lag in the hemodynamic response to the stimuli. A random effects general linear model (GLM) analysis was performed to create statistical parametric maps comparing the blood-oxygenation level dependent (BOLD) response during sequenced blocks to random blocks to delineate activations related to procedural learning trials. Since no cortical ROIs were identified a priori, the threshold for the cortex-based statistical analysis was set to $p<0.005$ and a cluster threshold of 6 voxels (162 mm^3 volume) was applied (Forman et al., 1995). A statistical threshold of $p<0.01$, uncorrected, was used to identify significant voxels within the subcortical ROI analysis. Comparisons between groups were limited to the clusters of voxels that differentiated sequenced from random blocks in either group, and the threshold was set to $p<0.05$.

3. Results

3.1. Serial Reaction Time Task

In the prescan phase, there was no difference in accuracy between the two groups, and no difference in accuracy within either group over the five blocks of sequenced trials. Median RT showed significant positive skew that was corrected with log transformation. The analysis of variance revealed a main effect of block, $F(2.36, 51.86)=4.25$, $p=0.015$, characterized by faster RT over the course of the five blocks (Fig. 1). There was a non-significant trend towards slower RT in the patient group, $F(1,22)=2.66$, $p=0.117$. Group did not interact with block, suggesting relatively equivalent improvement over the course of the five blocks, also apparent in the similarity of the difference scores between blocks 1 and 5, $t(22)=0.63$, $p=0.537$.

In the scanning phase, accuracy was better on sequenced than random trials in the schizophrenia sample (95% versus 93%, Wilcoxon $Z=2.81$, $p=0.005$), and a similar trend was apparent in the control sample (98% vs. 97%, Wilcoxon $Z=1.80$, $p=0.072$). A main effect of condition was apparent for the log transformed median RT scores, $F(1,22)=28.67$, $p<0.001$, characterized by faster RTs on the sequenced trials relative to the random trials, suggesting a significant procedural learning effect that exceeds gains attributable to a general improvement of motor speed with practice (Fig. 1). The schizophrenia sample showed a trend toward slower RT than the control group, $F(1,22)=3.71$, $p=0.067$. There was no significant effect of block, nor was there an interaction between block and condition, suggesting that most of the procedural learning occurred in the orientation phase. Group also did not interact with condition, block, or condition and block, suggesting no difference in procedural learning between the schizophrenia and control groups. The magnitude of the difference in RT between sequenced and random blocks was similar in the two groups (i.e., controls $M=25.43$, S.D.=36.10 ms; patients $M=35.60$, S.D.=41.60 ms).

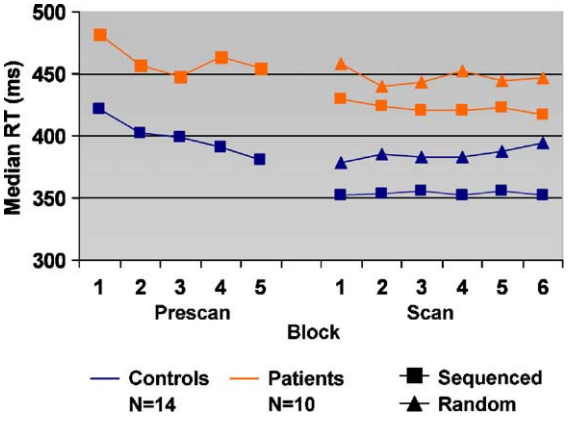

Fig. 1. Procedural learning in schizophrenia and normal controls.

Table 2
Regions of activation in the control and schizophrenia groups

Group	Brain region	Talairach coordinates			Max *t*	Size (mm^3)
		X	Y	Z		
Controls						
Cortex-based analysis						
PL>R	L. middle frontal gyrus (BA 6)	−31	8	50	5.12	351
	L. superior frontal gyrus (BA 9)	−20	42	35	5.46	432
	L. angular gyrus (BA 39)	−45	−65	24	5.18	945
	R./L. anterior cingulate (BA 24/32)	1	34	1	3.88	297
	L. inferior frontal gyrus (BA 47)	−49	26	−8	4.16	243
Sub-cortical ROI analysis						
PL>R	L. caudate body	−9	11	7	6.24	1728
	R. caudate body	13	20	6	4.31	324
	R. caudate body	8	3	6	4.51	693
	L. globus pallidus	−15	−10	−6	3.17	54
	R. putamen	30	−22	10	4.03	135
Schizophrenia						
Cortex-based analysis						
PL>R	R. anterior cingulate (BA 33)	3	12	22	6.66	216
	R. superior temporal gyrus (BA 38)	45	7	−19	5.72	5.13
R>PL	R. superior frontal gyrus (BA 9)	21	44	32	7.10	189
	R. superior frontal gyrus (BA 10)	30	53	16	6.49	162
	R. middle frontal gyrus (BA 10)	31	58	8	4.96	945
	R. inferior frontal gyrus (BA 47)	34	25	1	9.90	378
Sub-cortical ROI analysis						
PL>R	R. putamen	16	5	6	3.51	81
	L. globus pallidus	−10	2	0	5.84	351
R>PL	L. caudate body	−12	−1	19	3.31	27

Analysis of correlations revealed no significant associations between either the prescan or the scanning measures of procedural learning and age or GAF scores in the combined sample, or in either patients or controls considered alone. Procedural learning was not related to years of education in the combined sample or the control sample, but a direct association was apparent for the scanning PL measure in the patient sample ($r=0.73$, $p=0.016$). The patients exhibited a relative advantage on sequenced compared to random trials that increased with education, but they did not show an association between procedural learning and the PANSS positive, negative, or general scores.

Fig. 2. Brain regions involved in procedural learning in controls. (A) Lateral surface of brain showing activations in frontal (superior frontal gyrus (BA 9) and premotor region (BA 6)) and parietal lobe (angular gyrus BA 39). (B) Sagittal slice showing activation in anterior cingulate (BA 24/32). (C) Axial slice through basal ganglia showing bilateral activations in caudate. Note: Left/right reversed on axial slice.

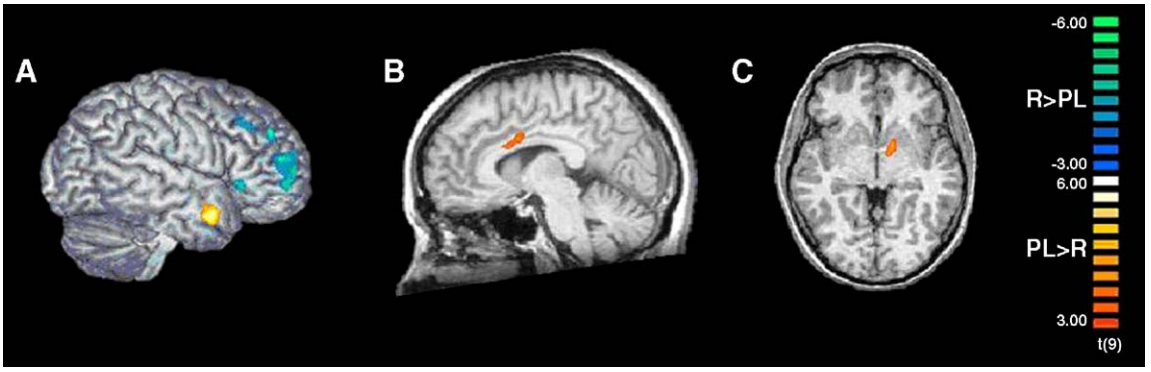

Fig. 3. Brain regions involved in procedural learning in schizophrenia. (A) Right lateral surface of cortex showing greater activity in right superior, middle and inferior gyri during random compared to sequenced (procedural learning) blocks. Right temporal lobe activation observed during sequenced blocks relative to random blocks. (B) Activity in anterior cingulate is greater during sequenced blocks. (C) Activity in left globus pallidus during sequenced blocks. Note: Right/left is reversed on axial slice.

3.2. Functional imaging results

The activations during the SRTT in the control and schizophrenia groups are presented in Table 2 and Figs. 2 and 3. In the control group, procedural learning on the sequenced trials was associated with greater activation of several structures of the dorsal striatum (bilateral caudate, left globus pallidus, right putamen), as well as bilateral anterior cingulate cortex, the left angular gyrus and several left frontal gyri (inferior, middle and superior). Procedural learning in the schizophrenia sample also activated the right dorsal anterior cingulate cortex and regions of the dorsal striatum (right putamen and left globus pallidus), but, unlike the control group, procedural learning also activated the right superior temporal gyrus, and failed to activate the caudate nucleus, the left angular gyrus, the left anterior cingulate or the left frontal cortex. Also atypical were the schizophrenia group activations during random trials compared to sequenced trials in the superior, middle and inferior gyri of the right frontal lobe and the left caudate.

Differences in activation elicited from sequenced blocks relative to random blocks revealed significantly greater activations during procedural learning in the control group compared to the schizophrenia group in multiple regions of the right frontal lobe, as well as activation in the left superior frontal gyrus, left angular gyrus and bilateral caudate (Table 3 and Fig. 4). The schizophrenia group exhibited greater activations than

Table 3
Group differences in activation

Group	Brain region	Talairach coordinates			Max t	Size (mm^3)
		X	Y	Z		
Controls>schizophrenia	L. superior frontal gyrus (BA 9)	−20	42	35	4.81	378
	R. superior frontal gyrus (BA 9)	20	44	34	2.42	54
	R. superior frontal gyrus (BA 10)	18	59	16	3.12	81
	R. superior frontal gyrus (BA 10)	31	51	16	2.35	81
	R. middle frontal gyrus (BA 10)	35	57	9	3.02	297
	R. middle frontal gyrus (BA 10)	36	53	0	3.30	108
	R. inferior frontal gyrus (BA 47)	34	25	1	4.33	378
	L. angular gyrus (BA 39)	−43	−65	19	3.32	216
	L. caudate body	−12	8	13	2.15	27
	L. caudate body	−10	−1	19	2.60	54
	L. caudate body	−15	5	19	2.91	27
	R. caudate body	12	22	6	3.60	216
Schizophrenia>controls	R. anterior cingulate (BA 33)	3	11	22	2.30	27
	L. globus pallidus	−9	−2	−2	2.40	54
	R. superior temporal gyrus (BA 38)	42	8	−17	2.08	27
	R. superior temporal gyrus (BA 38)	48	8	−15	2.18	54

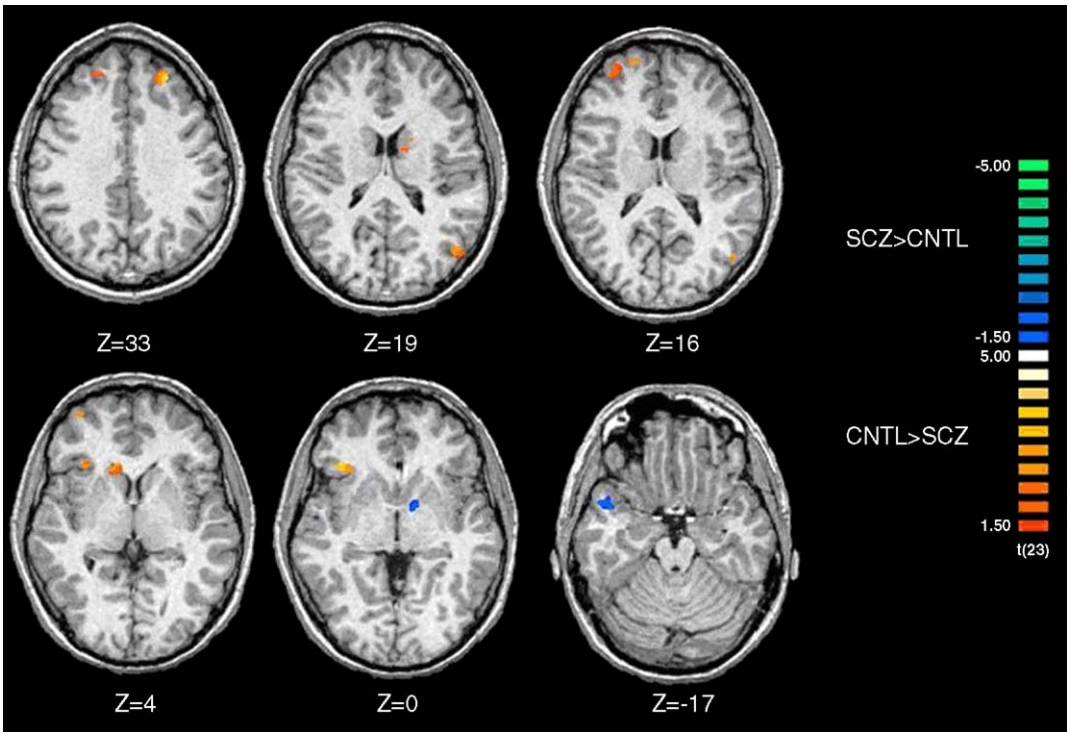

Fig. 4. Group differences in procedural learning activations. Controls demonstrate greater activity in several prefrontal and basal ganglia regions. Controls also demonstrate greater activity during sequenced (procedural learning) blocks in parietal area 39. Schizophrenia patients demonstrate greater activity in right temporal lobe and left basal ganglia during sequenced blocks than controls. Note: Right/left is reversed on axial slices.

the control group during procedural learning in the right anterior cingulate, the left globus pallidus and the right superior temporal gyrus (Fig. 4).

4. Discussion

The SRTT elicited similar procedural learning but dissimilar hemodynamic activations in medicated chronic patients with schizophrenia relative to an age-matched healthy control group. The similarities between groups in the learning curves and the magnitude of acquired procedural learning on the SRTT are consistent with one recent report (Exner et al., 2006), but inconsistent with two previous reports (Green et al., 1997; Kumari et al., 2002). The discrepancy may relate to less exposure to typical neuroleptic medications, increased exposure to the sequenced stimuli, less severe psychotic symptoms or perhaps to the higher educational level of the schizophrenia patients in the present and past report of a sparing of SRTT procedural learning. The hemodynamic response of the control group was very different from the schizophrenia group, but the areas of activation were consistent with prior normal control groups from fMRI and PET investigations of SRTT procedural learning that exhibited reliable activations in the dorsal striatum, the anterior cingulate, the parietal cortex and the frontal cortex (Grafton et al., 1995; Peigneux et al., 2000; Rauch et al., 1995, 1997a,b; Willingham, 1997). In contrast, procedural learning in the schizophrenia sample relative to the control sample elicited less activation in bilateral frontal, left angular and bilateral caudate regions, along with an unusual excess activation of the right superior temporal cortex, right anterior cingulate cortex and left globus pallidum, results that replicate and extend the observation of circumscribed activation of the left inferior frontal gyrus reported in the only prior investigation of SRTT procedural learning activations on fMRI in schizophrenia (Kumari et al., 2002). The greater use of typical antipsychotic medications and the absence of procedural learning in the prior study may account for the divergent pattern of cortical activations and the much more pronounced subcortical deficit noted here, and perhaps the unusual activation of the right temporal lobe as well. If replicated, the absence of normal cortical activation in schizophrenia may suggest a disease-relevant cerebral dysfunction, whereas excess activation of the right superior temporal gyrus, right anterior cingulate and left globus pallidus may represent compensatory activations early in development to overcome limitations imposed by the dysfunctional regions. A

similar mechanism was recently described for atypical fMRI activations relating to Huntington's disease (Paulsen et al., 2004), consistent with speculated neurodevelopmental involvement of motor circuits in schizophrenia (e.g. Caligiuri and Lohr, 1994). Alternately, excess procedural learning induced activation of the mesial temporal cortex in patients suffering from obsessive compulsive disorder was previously interpreted to result from engagement of declarative memory processes (Rauch et al., 1997a,b). The mesial temporal cortex is more relevant to declarative memory processes than the superior temporal cortex, but the excess activation of the latter in the schizophrenia sample is sufficient to encourage an independent assessment of explicit retrieval strategies in future investigations.

The present results are readily assimilated within models of subcortico-cortical circuitry dysfunction in schizophrenia and may offer additional regional specificity. The basal ganglia are related to cortical structures through at least five anatomically and functionally distinct circuits with highly organized fiber connections generally depicted as the motor, oculomotor, dosolateral frontal, limbic and orbitofrontal circuits (Alexander and Crutcher, 1990). Procedural learning depends on the integrity of more than one of these circuits and the demands on a particular circuit will vary over the course of the learning experience. For example, additional activation of the motor circuit was exhibited in both the normal control and the schizophrenia samples during procedural learning, but the latter exhibited a relative dysfunction in regions typically attributed to the dorsolateral frontal, limbic or orbitofrontal circuits. Also, procedural learning activations in the control group exhibited left hemisphere preponderance not apparent in the schizophrenia sample, a discrepancy consistent with observations from motor and sensory examinations suggesting greater dysfunction in the left cerebral hemisphere in schizophrenia (Purdon and Flor-Henry, 2000; Purdon et al., 2001). Further refinement will be dependent on the exclusion of the medication effects on procedural learning (Bedard et al., 1996; Purdon et al., 2003; Scherer et al., 2004; Stevens et al., 2002). Although medications alone cannot explain all of the motor impairments associated with schizophrenia (Caligiuri and Lohr, 1994), they provide a viable counterhypothesis for transient procedural learning deficits that may therefore not reflect a disease-related neuropathology (Stevens et al., 2002). The current demonstration included fewer patients receiving typical antipsychotic medications than prior demonstrations with contrary results (Green et al., 1997; Kumari et al., 2002), but a more direct assessment of medications will be necessary for delineation of disease-specific cerebral pathology in schizophrenia. Further refinement of the model will also require more sophisticated methods to quantify and exclude contributions from declarative memory. Although the embedded sequence of the SRTT rarely becomes available to conscious awareness even after many blocks of trials (Destrebecqz and Cleeremans, 2001), and informal debriefing in the current study revealed no recognition of the sequence, an attribution of the right temporal lobe activation to an early compensatory mechanism will require formal exclusion of declarative memory processes.

Consistent with other methods of quantifying procedural learning, the embedded series SRTT is capable of eliciting procedural learning in schizophrenia, and a reliable pattern of activation in healthy control subjects, though the cerebral activation associated with procedural learning in schizophrenia is abnormal. The localization of the cerebral dysfunction and the apparent compensatory hyperactivation offers additional specificity to further fMRI investigation with improved control of medications and declarative memory processes. For example, more tightly controlled applications of this method to first episode patients and their relatives will facilitate assessment of the sensitivity and specificity of the apparent compensatory activation as a physiological endophenotype for the illness with considerable value to early diagnosis and genetic models for schizophrenia. Also, the general and robust cognitive impairment observed in schizophrenia is a significant impediment to vocational and occupational reintegration, with few skills remaining intact after the onset of illness. It is reasonable to assume that procedural learning could provide a foundation for higher level intellectual skills (e.g. Rizzolatti and Arbib, 1999), with a disruption of this basic process contributing to a general cognitive deficit similar to that observed in schizophrenia. Although the behavioral output was relatively normal, the cerebral physiology underlying this output was highly irregular, perhaps suggesting atypical cerebral recruitment or a disruption of the normal transitions between neural circuits responsible for moving from serial to parallel processes (e.g. Hikosaka et al., 1999). The current investigation demonstrated an abnormal hemodynamic response at the end of this process, after instantiation of procedural learning. It would now be useful to delineate further the stage of the learning process that is disrupted, in hopes of developing strategies for remediation that might avoid the disruption of higher cognitive processes that produce the significant vocational debilitation associated with schizophrenia.

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