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Procedural Learning in First Episode Schizophrenia Investigated With Functional Magnetic Resonance Imaging

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Objective: The present investigation assessed the severity, course, and cerebral implications of serial reaction time (SRT) procedural learning deficits in schizophrenia. ***Method:*** Hemodynamic changes on fMRI were assessed during an SRT task in 17 unmedicated first episode psychosis (FEP) patients and matched healthy controls. ***Results:*** The groups demonstrated comparable procedural learning and associated activation of anterior cingulate cortex, subcortical structures, and many left frontal structures. The groups also demonstrated comparable increased activation of right parietal structures on trials with demands for spatial localization without procedural memory. Relative to healthy controls, the schizophrenia sample showed less activation of one region of the left middle frontal cortex and more activation of left superior temporal cortex on procedural trials, but more activation of right medial frontal cortex on localization trials. ***Conclusions:*** Intact SRT procedural learning and normal or enhanced hemodynamic response in subcortical and right cortical structures diverges from prior results with medicated samples, suggesting a more focal cerebral dysfunction in the left middle frontal cortex before the onset of treatment.

Keywords: schizophrenia, first episode psychosis, fMRI, procedural learning, serial response time task

Schizophrenia is characterized by a wide range of cognitive deficits (Heinrichs & Zakzanis, 2002) that appear before the onset of active symptoms of psychosis (Fuller, Nopolulos, Arndt, O'Leary, Ho, & Andreasen, 2002), show small improvements from medications (Woodward, Purdon, Meltzer, & Zald, 2005), and represent a persistent impediment to psychosocial rehabilitation (Matza, Brewster, Revicki, Zhao, Purdon, & Buchanan, 2006). The deficits have been associated with diffuse cerebral pathology, occasionally with a left hemisphere emphasis, by investigations of structural, functional, and metabolic abnormalities (e.g., Bleich-Cohen, Hendler, Kotler, & Strous, 2009; Harrison, 1999; Janssen et al., 2009; Laruelle, Abi-Dargham, Gil, Kegeles, & Innis, 1999).

It has been suggested that this diffuse pattern of cognitive impairments and cerebral pathology may relate to abnormal development of the basal ganglia that disrupts striato-thalamo-cortical circuits necessary for motor, sensory, and cognitive functions (Kliest, 1960; Mettler, 1955; Pantelis, Barnes, & Nelson, 1992; Seger, 1994). There have been intermittent MRI reports of young neuroleptic naïve individuals with schizophrenia showing volume reductions of the caudate, but the results have not been uniform and several studies have documented basal ganglia changes with antipsychotic treatment (Brandt & Bonelli, 2008; Keshavan, Rosenberg, Sweeney, & Pettegrew, 1998; Shenton, Dickey, Frumin, & McCarley, 2001). Several investigations have also reported cortical asymmetrical shifts between left to right hemisphere dysfunction with medication (e.g., Purdon & Flor-Henry, 2000; Purdon, Woodward, & Flor-Henry, 2001; Seidman et al., 1993; Tomer & Flor-Henry, 1989; Tomer, 1989). Thus, it is unclear if the basal ganglia pathology presumed responsible for diffuse cortical dysfunction and associated behavioral anomalies in schizophrenia precedes disease onset, or if it occurs as a result of treatment and/or other factors associated with disease progression.

Procedural learning tasks may offer a behavioral assay sensitive to the distinction between developmental and acquired deficits. Procedural learning is dependent on the integrity of the basal ganglia, and results from nonintentional encoding of redundant associations through repetition, proximity or practice (Anderson, 1976; Cohen & Squire, 1980; Reber, 1989; Seger, 1994; Squire, 1986). Contrasted with the conscious acquisition and recollection of declarative memory, procedural learning is implicitly acquired through entrenchment of associated procedures. It is manifest through improvements in motor and cognitive skills not typically amenable to verbal declaration. A double-dissociation model has been proposed attributing procedural deficits to basal ganglia dysfunction, and declarative deficits to temporal lobe dysfunction (e.g., Knowlton, Squire, & Gluck, 1994; Martone, Butters, Payne, Becker, & Sax, 1984; Pascual-Leone et al., 1993; Saint-Cyr, Taylor, & Lang, 1988).

Clinical comparative evidence consistent with a double dissociation has been supplemented with neuroimaging studies resulting from adaptations of an embedded series serial reaction time (SRT) task (Hebb, 1967; Nissen & Bullemer, 1987). The SRT task entails

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a rapid presentation of a series of visual stimuli, and measurement of the time required for a simple motor response. The target appears in one of four spatial positions and the response is a button depression from a corresponding finger. In the embedded series variant, a predefined order of stimuli is repeated several times before a randomly ordered series of stimuli, with faster reaction times (RTs) on successive sequenced trials indicative of combined motor and procedural learning, and faster RTs on sequenced relative to random trials indicative of procedural learning.

Functional MRI studies that have compared the blood oxygen level dependent (BOLD) response on sequenced trials relative to random trials have consistently reported an association between procedural learning and a greater BOLD response in the dorsal striatum (i.e., caudate and putamen), anterior cingulate cortex, prefrontal cortex (often in the left hemisphere), premotor cortex, and inferior parietal cortex (Kumari et al., 2002; Martis, Wright, McMullin, Shin, & Rauch, 2004; Rauch et al., 1997; Reiss et al., 2005, 2006; Strangman, Heindel, Anderson, & Sutton, 2005; Willingham, Salidis, & Gabrieli, 2002; Zedkova et al., 2006). Consistent with the double-dissociation model, differential activation of the medial temporal lobe during SRT procedural learning is rarely reported (Foerde et al., 2008). Distinct patterns of subcortical activation have been noted, however, with a caudate—dorsolateral prefrontal loop engaged primarily during skill acquisition, and a putamen—supplementary motor cortex loop engaged during both acquisition and maintenance (e.g., Jueptner et al., 1997a, 1997b; Poldrack, Sabb, Foerde, Tom, Asarnow, Bookheimer, & Knowlton, 2006).

The SRT procedural learning paradigm paired with functional neuroimaging may be uniquely suited to examination of the nature and severity of putative basal ganglia dysfunction in schizophrenia, but the results to date have been ambiguous. A recent meta-analysis noted evidence of procedural learning in the faster RTs on sequenced trials relative to random trials in both schizophrenia and healthy control samples, but the magnitude of the procedural learning RT advantage was smaller in the schizophrenia samples (Siegert, Weatherall, & Bell, 2008). This lead some to infer spared basal ganglia in schizophrenia from the presence of procedural learning (e.g., Foerde et al., 2008), and others to infer basal ganglia dysfunction from the reduced magnitude of procedural learning (e.g., Pedersen et al., 2008).

Additional ambiguity has resulted from a lack of consideration of potential mitigation from antipsychotic medications. There is overwhelming evidence of medication-related movement disorders resulting from disruption of basal ganglia structures (Kessler et al., 2006; Leucht et al., 2009), and SRT procedural learning is compromised by haloperidol in healthy control samples (Kumari et al., 1997). SRT investigations in schizophrenia have relied almost exclusively on medicated patients, precluding delineation of medication effects aside from noting that samples with larger representation of typical neuroleptics appear to exhibit more diffuse cortical and subcortical abnormalities on fMRI (Kumari et al., 2002; Reiss et al., 2006; Zedkova et al., 2006), and greater procedural learning impairment on SRT (Exner, Bouscein, Degener, & Irle, 2006; Exner, Weniger, Schmidt-Samoa, & Irle, 2006; Green, Kern, Williams, McGurk, & Kee, 1997; Kumari et al., 2002; Marvel et al., 2005; Pedersen et al., 2008; Reiss et al., 2006; Schwartz, Howard, Howard, Hovaguimian, & Deutsch, 2003; Stevens et al., 2002; Zedkova et al., 2006). The reliance on medicated samples thus limits meaningful inferences from existing SRT procedural learning data about basal ganglia pathology and its relevance to cortical dysfunction in schizophrenia.

The present investigation examined fMRI during SRT procedural learning in unmedicated or neuroleptic naive individuals early in the course of the illness. If medication contributed to previously reported procedural learning limitations and basal ganglia anomalies, then this unmedicated sample would be expected to show (1) no procedural learning impairment in the magnitude of the difference in RT on sequenced trials relative to random trials, and (2) relatively normal subcortical and cortical involvement during procedural learning, given by the magnitude of the BOLD signal changes on fMRI on sequenced relative to random trails. Similarly, if prior reports have confounded an hypothesized left cortical dysfunction related to illness development with a right cortical dysfunction related to illness progression or treatment, then the unmedicated sample would be expected to show (1) a compromise of left hemisphere cortical function apparent in a smaller magnitude of BOLD signal change on sequenced trials relative to random trials, compared to healthy controls, but (2) no compromise of right hemisphere cortical function.

Method

Participants

Eighteen patients within 1 year of the onset of their first episode of psychosis (FEP) and 19 healthy controls (HC), all between 18 and 35 years of age and right-handed, were recruited for this study. Three participants were excluded from analysis; two HC because of explicit recognition of the repeating pattern within the SRT, and one FEP because of head movement in the scanner. The HC were recruited through local newspaper advertisements and by word-of-mouth among staff and students at the University of Alberta where the study was approved by the Health Research Ethics Board. All participants provided written informed consent to participate. The FEP were recruited from the Edmonton Early Psychosis Intervention Clinic (EEPIC) of Alberta Hospital Edmonton. The clinical diagnosis was confirmed with a Structured Clinical Interview for *DSM–IV* Axis I Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 2005). Among the 17 FEP with usable data, 11 met criteria for schizophreniform disorder and 6 met criteria for schizophrenia (4 undifferentiated, 1 paranoid, 1 residual). Psychiatric symptoms and functional status were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) and the Global Assessment of Function Scale (SCID-GAF) administered by an EEPIC nurse or clinical psychologist after training to an intraclass correlation criteria greater than 0.79 on 12 patients corated by an experienced examiner. The PANSS and GAF scores for the FEP suggested a moderate severity of positive, negative and general syndromes of psychosis, and severe impairment of social functioning (see Table 1). GAF ratings on the HC were in the superior range, much higher than the ratings assigned to the FEP, $t(32) = 15.40$, $p < .01$. The FEP also had fewer years of education than the HC, $t(32) = 2.56$, $p = .02$, but they were equivalent in age, gender, and socioeconomic status (see Table 1). FEP participants were only eligible for inclusion if they had at least two active *DSM–IV–TR* symptoms of psychosis of more than one month but less than 12 months' duration. Participants were unmedicated at the time of the baseline assessment, had no prior

Table 1
Sample Characteristics[a]

Variable	Group	
	Healthy controls (n = 17)	First episode psychosis (n = 17)
Age (years)	22.12 (3.19)	21.94 (3.99)
Gender	13 M/4 F	13 M/4 F
Education (years)	15.00 (1.69)	13.18 (2.40)
Mean illness duration (years)		.38 (.27)
Mean medication exposure (days)		17.88 (25.38)
Neuroleptic niave		n = 4
PANSS[b] Positive		18.76 (4.41)
PANSS Negative		18.59 (4.00)
PANSS General		37.65 (7.37)
Global Assessment of Function (GAF)	92.94 (3.09)	46.29 (12.07)
Socio-Economic Status (SES)h	2.59 (.51)	2.53 (.64)

[a] Mean and (*SD*). [b] PANSS = Positive and Negative Syndrome Scale.

exposure to intramuscular antipsychotic medications, and their lifetime cumulative duration of exposure to oral antipsychotic medications was less than 90 days. Participants were ineligible if they reported a history of head injury or neurological disease, systemic medical disease likely to affect central nervous system functions, current substance abuse disorder, current or previous substance dependence disorder, or ferromagnetic objects in the body. HC participants were also excluded if they reported current or prior Axis I psychiatric disorders on the SCID, or a family history of schizophrenia on a pretest interview.

Serial RT Task

In the SRT task, participants were instructed to quickly and accurately identify the location of an asterisk that alternated between four boxes arranged horizontally on a computer screen (Nissen & Bullemer, 1987; Rauch et al., 1997; Woodward et al., 2007; Zedkova et al., 2006). Participants responded by pressing one of four response keys that corresponded to the location of the asterisk, using the middle and index finger of each hand. In the scanning phase, each block consisted of 60 trials of either sequenced (S) or random (R) stimuli, and each of the 6 blocks of random trials was followed by one of the 6 blocks of sequenced trials. Within sequenced blocks, the location of the asterisk followed a 12-element second order conditional (SOC) sequence corresponding to positions 3–4–2–3–1–2–1–4–3–2–4–1 that repeated five times. SOC sequences require two elements of temporal context to predict the location of the next stimulus (e.g., asterisk), and they have been shown to protect against the formation of explicit knowledge during SRT tasks, even after extended practice (Destrebecqz & Cleeremans, 2001; Reed & Johnson, 1994). Within the random blocks the location of the asterisk was pseudorandomly assigned with the caveats that all 4 locations appeared with equal frequency within a block, and no location was repeated consecutively. On each trial the asterisk appeared for 800 ms before a 200 ms intertrial interval with an 18 s fixation point resting period after each block. Before entering the scanner, participants completed a practice session consisting of 5 blocks of 72 sequenced trials. Once in the scanner, participants completed two scanning runs, each consisting of 3 sequenced and 3 random blocks that alternated in a blocked AB manner.

Separate analyses were undertaken for accuracy and response times in the prescan and scanned blocks of trials. A high rate of accuracy and associated negative skew was anticipated, necessitating nonparametric evaluation. In the prescan phase overall accuracy was compared between groups before within group examination of accuracy over the course of the 5 blocks of trials. In the scanning phase, groups were compared on overall accuracy as well as accuracy on sequenced trials and accuracy on random trials before within group evaluation over the course of the 6 blocks of trials. The analysis of RT in the prescan phase was primarily concerned with the anticipated reduction in response time resulting from repeated exposure to the five sequenced blocks of trials, representing a measure of total learning that includes both procedural learning and motor skill learning. In the scanning phase, the critical comparison concerned the anticipated response time advantage from blocks of sequenced trials relative to blocks of random trials, with the advantage providing a measure of procedural learning. The median RTs for each block were subjected to analysis of variance (ANOVA) before and after log-transformation to adjust for positive skew; the results did not differ and therefore only the uncorrected data are reported here. In the prescan analysis, this entailed a 5 (block) $\times$ 2 (group: HC, FEP) ANOVA with block as a within-subjects variable and group as a between-subjects variable, followed by a between group comparison of the magnitude of total (procedural and motor) learning with a between groups t test of the change in RT between blocks 1 and 5. Analysis of the scanned data entailed a 6 (block) $\times$ 2 (condition: sequenced, random) $\times$ 2 (group: HC, FEP) ANOVA with block and condition as within-subjects variables, again followed by between groups comparison of the magnitude of procedural learning given by the difference in RT between the sequenced and random trials. This difference score was also applied to a median split binary stratification of the sample to explore anticipated convergence between the magnitude of procedural learning and cerebral regions of interest implicated in the functional MRI analyses; this method was preferred over

analysis of correlations that tend to produce idiosyncratic associations in small samples that are oversensitive to RT outliers.

Functional MRI

All structural and functional MRI (fMRI) images were acquired during a single session on a Siemens Sonata 1.5T scanner located at the University of Alberta IN Vivo Imaging Center, and all image processing and statistical analyses were undertaken with Brainvoyager QX (Goebel & Jansma, 2004). Twenty-five contiguous axial (approximate range Z = 70 to Z = −30) 4 mm thick functional slices 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 = 3,000 ms). During each of the two runs 159 volumes were acquired and the first three volumes of each run were discarded. A high resolution, 144 slice, 1 × 1 × 1 mm voxel size 3D structural image was also acquired using an MPRAGE sequence. Motion correction, slice scan timing correction, spatial smoothing (8 mm FWHM), and linear and nonlinear temporal signal drift removal were applied to the raw fMRI images before statistical analysis. The functional images for each subject were then coregistered to their respective structural image using a two step semiautomated method that first utilized scanner positioning header data to align the images and then applied a multiscale intensity gradient for a more refined alignment. The coregistration parameters were obtained after motion correction had been applied to the raw fMRI images, but before spatial smoothing was carried out to maximize mutual information contained within the images. Following coregistration, the structural brain image for each subject was warped into standard Talairach space (Talairach & Tournoux, 1988) and functional data were interpolated to a voxel size of 3 × 3 × 3 mm.

Each subject's functional time course data were modeled at each voxel using a boxcar function with sequenced and random blocks entered as predictors and convolved with a gamma function to account for lag in the hemodynamic response before aggregation within a series of random effects General Linear Model (GLM) analyses, corrected for serial autocorrelation, to produce statistical parametric maps relevant to comparisons between conditions and groups. The maps resulting from fMRI comparisons are derived from a very large number of statistical comparisons that will increase the likelihood of significant but spurious results. In an effort to strike a reasonable balance between the risk of a Type I and a Type II error, the current analysis applied random effects GLM analyses with a threshold $p < .005$ (uncorrected), and a minimum cluster threshold of 6 voxels (162 mm^3 volume). The fMRI analyses entailed a multisubject multistudy application of three GLM to detect BOLD signal changes relevant to experimental condition (sequenced trials (SEQ) relative to random trials (RAN), collapsed across groups), group (FEP vs. HC, collapsed across condition), and the interaction between condition and group. Each region of interest, defined by a cluster of contiguous voxels that met the criteria above was subjected to ROI-specific GLM for extraction of beta weights of BOLD (percent signal) changes on sequenced trials relative to fixation (SEQrF) and random trials relative to fixation (RANrF) for calculation of effect sizes. The extracted beta weights were also subjected to supplemental comparisons of high and low magnitude procedural learning groups, and to an analysis of correlations between BOLD signal change in condition-relevant subcortical regions and the cortical regions with condition by group interactions.

Results

Serial RT Task

Accuracy was high for both groups in the prescan and scanned trials. On prescan trials the FEP group (89% hits) was less accurate than the HC group (96% hits), $U = 82.00$, $p = .03$. Accuracy showed no significant change over 5 blocks of trials in either the FEP, $\chi^2(4, N = 17) = 1.19$, $p = .88$, or the HC groups, $\chi^2(4, N = 17) = 6.86$, $p = .14$. In the scanned trials, the FEP group was again less accurate than the HC group on sequenced (FEP = 96% vs. HC = 99%), $U = 76.00$, $p = .02$, and random (FEP = 94% vs. HC = 97%) trials, $U = 75.00$, $p = .02$. Within group analyses revealed that the FEP and HC groups were both more accurate on sequenced trials compared to random trials (Wilcoxon signed-ranks test, FEP $Z = -3.62$, $p < .01$; HC $Z = -3.59$, $p < .01$). Accuracy remained constant over the 6 blocks of sequenced trials in the FEP, $\chi^2(5, N = 17) = 4.18$, $p = .52$, and the HC, $\chi^2(5, N = 17) = 4.78$, $p = .44$, and in the 6 blocks of random trials in the FEP, $\chi^2(5, N = 17) = 2.75$, $p = .74$, and the HC, $\chi^2(5, N = 17) = 5.33$, $p = .38$.

Median RTs from each block of prescan trials were subjected to ANOVA with group (FEP, HC) as a between-subjects variable and block (1 to 5) as a within-subjects variable (see Figure 1). RTs were slower in the FEP ($M = 444.50$, $SD = 85.03$ ms) than the HC ($M = 352.76$, $SD = 36.35$ ms), $F(1, 32) = 16.73$, $p < .01$, $\eta^2 = 0.34$. A main effect of block was also observed, $F(4, 128) = 5.84$, $p < .01$, $\eta^2 = .15$, and attributed by contrast comparisons to a linear decrease in RT over the 5 blocks of trials, $F(1, 32) = 13.86$, $p < .01$, $\eta^2 = .15$. There was no interaction between group and block, suggesting no significant disparity between groups in the linear decrease in RT over the 5 blocks. A between groups comparison of total learning scores (i.e., block 1 median RT - minus block 5) also gave no indication of a significant disparity between the improvement apparent in the FEP ($M = 28.68$, $SD = 44.69$ ms) and the HC ($M = 24.53$, $SD = 38.25$ ms), $t(32) = .29$, $p = .77$, $d = .07$.

Median RTs from each block of scanned trials were subjected to ANOVA with condition (random, sequenced) and block (1 through 6) as within subject variables, and group membership (FEP, HC) as a between-subjects variable. Main effects were obtained for condition, $F(1, 32) = 62.55$, $p < .01$, $\eta^2 = .36$, block, $F(5, 160) = 4.17$, $p = .01$, $\eta^2 = .07$ and group, $F(1, 32) = 8.96$, $p < .01$, $\eta^2 = .22$. There was no two way interaction between condition and group, or between condition and block, and there was no three way interaction between condition, block and group, $F(1, 32) = 1.12$, $p = .352$, $\eta^2 = .01$. A two-way interaction was observed between group and block, $F(5, 160) = 3.98$, $p < .01$, $\eta^2 = .19$. The main effect of condition resulted from faster RTs to sequenced items ($M = 346.64$, $SD = 55.37$ ms) compared to random items ($M = 372.24$, $SD = 57.91$ ms), $d = .09$. This RT advantage suggesting procedural learning was apparent for both the FEP (M Difference = 26.52, $SD = 22.96$ ms) and the HC (M Difference = 24.58, $SD = 13.61$), and no difference was observed between groups, $t(32) = 0.31$, $p = .76$. The main effect of group resulted from faster RTs in the HC compared to the FEP (HC: $M =$

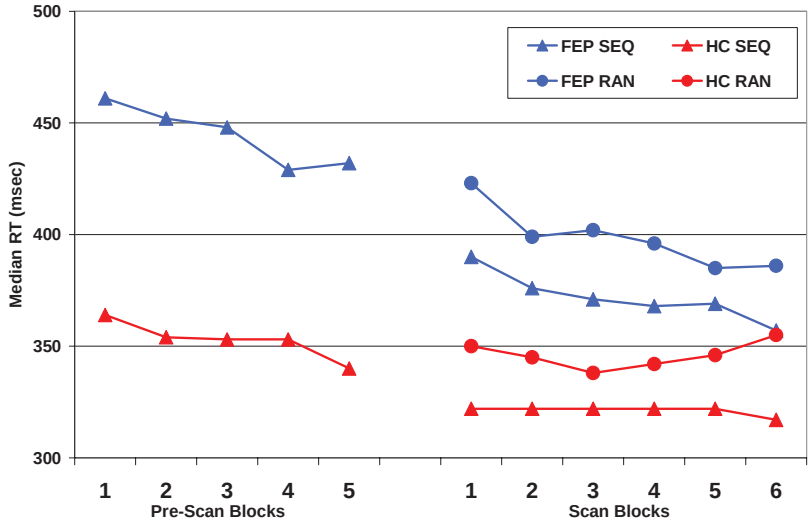

Figure 1. Median RTs for HCs ($n = 17$) and first episode psychosis ($n = 17$) during the SRT task. *Note:* Median RT (milliseconds) within each block of trials in the prescan and scanned blocks of trials. FEP = First Episode Psychosis ($n = 17$); HC = Healthy Controls ($n = 17$); SEQ = Sequenced Trials; RAN = Random Trials.

333.69, $SD = 28.33$ ms vs. FEP: $M = 385.19$, $SD = 66.36$ ms), $d = 1.01$. The interaction between block and group resulted from improved RTs over successive blocks in the FEP (Block 1 $M = 406.74$, $SD = 76.82$, Block 6 $M = 371.74$, $SD = 61.94$), $t(16) = 3.19$, $p < .01$, $d = .55$, not apparent in the HC. The FEP improvement was apparent in both the random trials (M change from Block 1 to Block 6 = 37.18, $SD = 50.24$ ms), $t(16) = 3.05$, $p < .01$, $d = .47$, and the sequenced trials (Mean change = 32.82, $SD = 51.52$ ms), $t(16) = 2.63$, $p = .02$, $d = .41$, suggesting continued motor learning throughout the scanning phase. Analysis of correlations revealed no significant association between the magnitude of procedural learning (i.e., median RT on scanned sequenced trials–random trials) in HC, FEP or the combined sample, and any of the demographic or clinical variables.

Functional Imaging Results

Random effects GLM analyses were undertaken to assess BOLD signal changes related to (1) experimental condition (SEQ vs. RAN), combining across group, (2) group (FEP vs. HC), combining across condition, and (3) the interaction between condition and group. The between condition comparison revealed greater SEQ than RAN signal change in three subcortical regions—with a cluster-wise center of gravity (COG) at the left caudate head, left putamen, right medial globus pallidus, and five cortical regions—with a COG at the midline anterior cingulate cortex, right anterior cingulate cortex, left inferior frontal gyrus, left middle frontal gyrus, and left superior frontal gyrus (see Table 2). RAN signal changes did not exceed SEQ changes in subcortical or left cortical structures, but RAN changes exceeded SEQ changes in five cortical regions of the right hemisphere—with a COG at the precentral frontal gyrus and four regions in the parietal lobe. The effect size for each significant ROI was estimated by subjecting the beta weights of BOLD (percent signal) changes on sequenced trials relative to fixation trials (SEQrF), and random trials relative to fixation trials (RANrF), to a group (between; FEP, HC) by condition (within; SEQrF, RANrF) ANOVA. This subsidiary analysis gave no indication of trends toward group differences or interactions; the profile of cerebral activations that differentiated SEQrF from RANrF trials was not unique to either group.

To examine further the relevance of the brain regions identified by the between condition multistudy GLM to procedural learning (PL), a series of t tests were applied to compare the ROI derived beta weights of subjects with low PL to subjects with high PL (see Table 3). FEP and HC were equally represented in the low and high PL groups (FEP $n = 8, 9$; HC $n = 9, 8$). The high PL group showed greater SEQrF relative to RANrF signal change in all three identified subcortical regions, all three left frontal lobe regions, and the midline region of the anterior cingulate cortex (all $p < .01$), along with a trend in the right anterior cingulate cortex. The low PL group showed a relative increase in signal change during SEQrF only in the midline ACC. The relation between magnitude of PL and signal change in the right hemisphere regions was less clear; RANrF exceeded SEQrF trials in the precentral frontal cortex and in four parietal lobe regions, but the magnitude of this discrepancy was only significant in the high PL group in one of the parietal regions ($p < .01$), with trends toward similar differences in other right hemisphere regions ($p < .05$) but no clear differentiation between the high and low PL groups.

No significant ROI was identified from the between groups multistudy GLM collapsing across experimental condition, but three significant ROI were detected in the group by condition analysis—with a COG in the left middle frontal, left superior temporal, and right medial frontal cortex (see Table 4). Subsidiary group by condition ANOVA of the beta weights extracted from these regions suggested small to medium effect sizes in the left middle frontal, $F(1, 32) = 14.73$, $p = .001$, $\eta^2 = 0.32$, left superior temporal, $F(1, 32) = 10.97$, $p = .002$, $\eta^2 = 0.26$, and medial frontal regions, $F(1, 32) = 9.66$, $p = .004$, $\eta^2 = 0.23$. The

Table 2

Brain Regions of Interest Identified by GLM of BOLD Signal Changes on fMRI Between Sequenced (SEQ) and Random (RAN) Trials, Combined Across Groups, and a Comparison of Beta Weights on Random Relative to Fixation Trials (RANrF), vs. Sequenced Relative to Fixation Trials (SEQrF) Within the First Episode Psychosis (FEP) and Healthy Control (HC) Groups[a]

			Talairach coordinates			ROI size		Beta			Effect size	Paired *t*-test
Brain region	H	BA	x	y	z	mm^2	Group	RANrF	SEQrF	RANrF-SEQrF	η^2	*p*
Caudate head	L		*−21*	*25*	*1*	189	ALL	.10 (.14)	.16 (.11)	−.06 (.11)	−.22	.004
							FEP	.11 (.14)	.17 (.11)	−.07 (.12)	−.24	.039
							HC	.10 (.15)	.15 (.12)	−.05 (.10)	−.21	.056
Putamen	L		*−13*	*7*	*5*	729	ALL	.16 (.15)	.22 (.18)	−.06 (.09)	−.31	.001
							FEP	.12 (.15)	.19 (.20)	−.07 (.09)	−.38	.007
							HC	.20 (.14)	.25 (.16)	−.04 (.08)	−.24	.041
Medial globus pallidum	R		*10*	*−2*	*4*	162	ALL	.02 (.23)	.11 (.22)	−.08 (.15)	−.24	.003
							FEP	−.05 (.28)	.05 (.25)	−.11 (.15)	−.35	.009
							HC	.10 (.14)	.16 (.17)	−.06 (.16)	−.13	.136
Anterior cingulate	M		*1*	*32*	*−1*	7587	ALL	.01 (.24)	.13 (.20)	−.12 (.12)	−.50	.000
							FEP	.04 (.23)	.13 (.19)	−.09 (.14)	−.30	.018
							HC	−.02 (.24)	.13 (.23)	−.15 (.10)	−.71	.000
Anterior cingulate	R		*5*	*41*	*11*	216	ALL	.11 (.23)	.18 (.23)	−.08 (.14)	−.23	.003
							FEP	.12 (.23)	.20 (.25)	−08 (.17)	−.20	.066
							HC	.09 (.24)	.16 (.21)	−.07 (.11)	−.31	.017
Inferior frontal	L	46	*−48*	*32*	*7*	270	ALL	.13 (.33)	.22 (.38)	−.09 (.13)	−.32	.001
							FEP	.12 (.38)	.17 (.42)	−.05 (.11)	−.19	.074
							HC	.24 (.29)	.26 (.35)	−.12 (.14)	−.42	.003
Middle frontal	L	6	*−35*	*3*	*45*	351	ALL	.16 (.19)	.22 (.18)	−.05 (.09)	−.30	.001
							FEP	.21 (.24)	.25 (.23)	−.03 (.09)	−.14	.120
							HC	.11 (.10)	.18 (.10)	−.07 (.08)	−.46	.002
Superior frontal	L	6	*−21*	*14*	*51*	189	ALL	.05 (.15)	.11 (.14)	−.06 (.11)	−.26	.003
							FEP	.05 (.17)	.08 (.14)	−.03 (.11)	−.07	.291
							HC	.05 (.15)	.14 (.13)	−.09 (.10)	−.48	.002
Precuneus parietal	R	7	4	−68	46	324	ALL	.21 (.54)	.13 (.53)	.08 (.14)	.29	.001
							FEP	.36 (.64)	.26 (.63)	.09 (.10)	.45	.002
							HC	.07 (.39)	−.01 (.37)	.08 (.16)	.19	.071
Inferior parietal	R	40	51	−34	35	486	ALL	.14 (.23)	.09 (.25)	.05 (.08)	.28	.001
							FEP	.12 (.27)	.06 (.28)	.06 (.09)	.33	.013
							HC	.16 (.19)	.11 (.21)	.04 (.08)	.23	.046
Inferior parietal	R	40	45	−48	37	162	ALL	.16 (.25)	.11 (.28)	.05 (.09)	.24	.003
							FEP	.13 (.33)	.06 (.37)	.07 (.10)	.33	.013
							HC	.20 (.15)	.16 (.14)	.03 (.09)	.15	.119
Inferior parietal	R	40	38	−45	53	108	ALL	.31 (.31)	.24 (.31)	.07 (.12)	.23	.003
							FEP	.28 (.35)	.22 (.37)	.06 (.12)	.21	.055
							HC	.33 (.26)	.25 (.24)	.07 (.13)	.26	.032
Precentral frontal	R	6	45	−2	34	189	ALL	.21 (.20)	.16 (.21)	.05 (.10)	.24	.003
							FEP	.20 (.19)	.14 (.21)	.06 (.11)	.28	.025
							HC	.23 (.21)	.18 (.21)	.04 (.09)	.20	.063

[a] H = hemisphere; L = left; R = right; M = midline; BA = Brodmann's area. RANrF-SEQrF < 0 indicates more activation during SEQrF than RANrF; RANrF-SEQrF > 0 indicates more activation during RANrF than SEQrF. η^2 (Eta^2) = effect sizes derived from ROI GLM applied to beta weights extracted from clusters of voxels identified by whole brain GLM for condition with $p < .005$ (uncorrected). Talairach coordinates correspond to the 3-D center of gravity (COG) within each ROI cluster; relevant voxel activations within a given cluster are not limited to these coordinates, or to the associated brain region label that corresponds to gray matter nearest the COG coordinates.

left middle frontal cortex interaction resulted from more SEQrF relative to RANrF signal change in the HC group, not apparent in the FEP group (see Figure 2). The left superior temporal interaction resulted from more SEQrF than RANrF in the FEP group, not apparent in the HC group. The right medial frontal interaction resulted from more RANrF than SEQrF signal change in the FEP group, not apparent in the HC group. The group by condition interactions remained significant after entry of several performance measure covariates for procedural learning (RT discrepancy between random and sequenced trials during scanning), motor learning (RT discrepancy between the first and last block of random trials during scanning), and RT (average RT across all blocks of scanned trials). Plotting the beta weight differences between SEQrF and RANrF (i.e., RANrF-SEQrF) for the left middle frontal, left superior temporal, and right medial frontal regions against the left caudate, left putamen and right medial globus pallidum (see Figure 3) with Bonferroni correction ($p = .0028$ for 18 comparisons), suggested a direct association in the FEP between changes in activation in the left superior temporal cortex and left caudate ($r = .72$, $p = .0012$) and left putamen ($r = .77$, $p = .0003$), and trend associations in the right medial globus pallidum ($r = .51$, $p = .036$), whereas the HC associations were all

Table 3
Comparison of Beta Weights for Brain Regions With Significant Effects of Condition Between Groups With Low and High Magnitude of Procedural Learning[a]

Brain region	H	PL Group	Beta			Effect size	Paired *t*-test
			RANrF	SEQrF	RANrF-SEQrF	η^2	*p*
Caudate head	L	Low	0.09 (.13)	0.12 (0.13)	−0.03 (0.10)	−0.10	ns
		High	0.12 (.15)	0.20 (0.09)	−0.08 (0.11)[a]	−0.36	0.008
Putamen	L	Low	0.14 (0.15)	0.17 (0.15)	−0.03 (0.06)	−0.20	ns
		High	0.18 (.15)	0.27 (0.20)	−0.08 (0.10)	−0.42	0.004
Medial globus pallidus	R	Low	−0.01 (.29)	0.05 (0.25)	−0.06 (0.16)	−0.13	ns
		High	0.06 (.14)	0.17 (0.16)	−0.10 (0.14)	−0.36	0.009
Anterior cingulate	M	Low	0.01 (0.29)	0.10 (0.22)	−0.10 (0.15)	−0.35	0.010
		High	0.03 (0.18)	0.16 (0.19)	−0.13 (0.10)	−0.67	0.00004
Anterior cingulate	R	Low	0.08 (0.23)	0.13 (0.19)	−0.05 (0.13)	−0.15	ns
		High	0.14 (0.23)	0.24 (0.26)	−0.09 (0.15)	−0.31	0.016
Inferior frontal gyrus	L	Low	0.15 (0.24)	0.21 (0.34)	−0.06 (0.14)	−0.16	ns
		High	0.11 (0.42)	0.22 (0.43)	−0.11 (0.12)	−0.48	0.002
Middle frontal gyrus	L	Low	0.18 (0.19)	0.20 (0.18)	−0.02 (0.09)	−0.05	ns
		High	0.15 (0.20)	0.24 (0.18)	−0.09 (0.06)	−0.66	0.00004
Superior frontal gyrus	L	Low	0.06 (0.15)	0.08 (0.14)	−0.02 (0.10)	−0.04	ns
		High	0.04 (0.16)	0.14 (0.14)	−0.10 (0.09)	−0.52	0.001
Parietal lobe (precuneus)	R	Low	0.14 (0.46)	0.05 (0.46)	0.08 (0.14)	0.27	0.026
		High	0.29 (0.61)	0.20 (0.59)	0.09 (0.14)	0.30	0.019
Inferior parietal lobe	R	Low	0.14 (0.24)	0.09 (0.26)	0.05 (0.11)	0.19	ns
		High	0.14 (0.23)	0.08 (0.24)	0.05 (0.06)	0.45	0.002
Inferior parietal lobe	R	Low	0.19 (0.17)	0.13 (0.15)	0.06 (0.08)	0.38	0.006
		High	0.14 (0.32)	0.10 (0.27)	0.04 (0.10)	0.13	ns
Inferior parietal lobe	R	Low	0.32 (0.36)	0.24 (0.35)	0.07 (0.11)	0.34	0.011
		High	0.29 (0.25)	0.24 (0.28)	0.06 (0.14)	0.16	ns
Precentral frontal	R	Low	0.17 (0.21)	0.10 (0.20)	0.06 (0.11)	0.26	0.029
		High	0.26 (0.18)	0.22 (0.21)	0.04 (0.08)	0.22	ns

[a] PL = Procedural learning group (low = average RT difference between sequenced and random trials < 23 ms, high > 23 ms); H = hemisphere; L = left; R = right; M = midline; RANrF = Random relative to fixation; SEQrF = Sequenced relative to fixation. RANrF-SEQrF < 0 indicates more activation during SEQrF than RANrF, RANrF-SEQrF > 0 indicates more activation during RANrF than SEQrF. Talairach coordinates appear in Table 2. Brain region corresponds to the nearest gray matter to the 3-D center of gravity within the specified cluster of voxels; activations are not necessarily limited to that structure alone.

merely trends ($r = .31$; $r = .35$; $r = .23$, respectively). However, the HC showed significant correlations between left middle frontal cortex and left putamen ($r = .77$, $p = .0003$), and right medial globus pallidum ($r = .75$, $p = .0005$), and a trend association with the left caudate ($r = .63$, $p = .0071$), not apparent in the FEP ($r = .30$; $r = -0.14$, $r = -0.21$, respectively). The signal change to SEQrF relative to RANrF in the right medial frontal gyrus showed a trend toward a similar pattern of direct associations in the HC, not apparent in the FEP.

Discussion

The results of the current investigation constitute an initial step toward clarification of the severity, course, and cerebral implications of SRT procedural learning deficits in schizophrenia by measurement of fMRI hemodynamic changes in unmedicated patients. The SRT procedural learning deficits in schizophrenia suggested in a recent meta-analysis (Siegert, Weatherall, & Bell, 2008), as well as bilateral cortical and subcortical fMRI BOLD signal abnormalities during SRT procedural learning reviewed above, were not observed in the current sample. Unmedicated patients with a recent onset of schizophrenia and minimal prior exposure to antipsychotic medications demonstrated slower and less accurate choice RT, but no robust impairment of SRT procedural learning in either the within group or between groups comparisons. Increased BOLD signals were detected on sequenced trials relative to random trials in the left caudate, left putamen, left superior frontal, left inferior frontal gyrus, and left middle frontal gyrus, all of which have been reported in at least two prior investigations comparing sequenced to random trials in healthy control samples (Willingham et al., 2002), as well as the right medial globus pallidus, a large midline region with a center of gravity at the anterior cingulate cortex, and a smaller right hemisphere region of the anterior cingulate cortex. No between groups differences or interactions between groups and conditions were observed in these regions, and all but the right anterior cingulate demonstrated a dissociation between participants with low and high magnitude procedural learning. The unmedicated patients with a first episode of psychosis show activation of similar subcortical and cortical structures to healthy controls while engaged in a procedural memory task, and they do not exhibit SRT procedural learning deficits.

The unmedicated schizophrenia group was not exhibiting diffuse bilateral cortical pathology during SRT procedural learning. Rather, the differences between groups were limited to three cortical regions—left middle frontal, left superior temporal, and right medial frontal, only one of which suggested reduced activa-

Table 4

Brain Regions of Interest Identified by GLM of BOLD Signal Changes on FMRI With Interactions Between Condition (Sequenced (SEQ) vs. Random (RAN) Trials) and Group (FEP vs. HC), and a Comparison of Beta Weights on Random Relative to Fixation Trials (RANrF), vs. Sequenced Relative to Fixation Trials (SEQrF) Within the First Episode Psychosis (FEP) and Healthy Control (HC) Groups[a]

			Talairach coordinates			ROI		Beta			Paired *t*-test	Effect size
Brain region	H	BA	x	y	z	Voxels	Group	RANrF	SEQrF	RANrF-SEQrF	*p*	η^2
Superior temporal	L	22	−60	−46	13	189	ALL	.15 (.33)	.18 (.36)	−.03 (.17)	.384	−.03
							FEP	.07 (.37)	.19 (.23)	−.12 (.19)	.025	−.28
							HC	.23 (.27)	.17 (.24)	.06 (.11)	.030	.26
Middle frontal	L	6	−22	1	53	648	ALL	.14 (.19)	.16 (.18)	−.02 (.10)	.343	−.04
							FEP	.20 (.22)	.16 (.21)	.04 (.08)	.074	.19
							HC	.09 (.14)	.16 (.15)	−.07 (.08)	.003	−.44
Medial frontal	R	32	10	10	44	162	ALL	.24 (.25)	.21 (.21)	.02 (.10)	.168	.07
							FEP	.30 (.33)	.23 (.29)	.07 (.10)	.007	.37
							HC	.17 (.10)	.19 (.09)	−.02 (.08)	.254	−.08

[a] H = hemisphere; L = left; R = right; M = midline; BA = Brodmann's area. RANrF-SEQrF < 0 indicate more activation during SEQrF than RANrF, RANrF-SEQrF > 0 indicates more activation during RANrF than SEQrF. η^2 (Eta^2) = effect sizes derived from a ROI GLM applied to beta weights extracted from whole brain GLM for group by condition with $p < .005$ (uncorrected). Talairach coordinates correspond to the 3-D center of gravity (COG) within each ROI cluster; relevant voxel activations within a given cluster are not limited to these coordinates, or to the associated brain region label that corresponds to gray matter nearest the COG coordinates.

tion potentially indicative of cerebral dysfunction. Relative to controls, the patients showed less activation of left middle frontal cortex, and less convergence between this activation and activation of subcortical structures. In contrast, again relative to the healthy control sample, the patients showed more activation of left superior temporal cortex, and more convergence between activation of this structure and activation of the subcortical regions. The left middle frontal dysfunction is in line with a priori predictions of left hemisphere pathology associated with schizophrenia that predates the onset of medication or the progression of illness, but the greater engagement of left superior temporal cortex, and the strong association between this region and subcortical structures, was not predicted. The latter may suggest compensatory engagement of cortex proximal to the inferior frontal dysfunction during the procedural learning task responsible for the relatively intact SRT procedural learning, similar to subcortical compensatory activation proposed to account for gradients of cortical activation and neurological soft signs apparent in high risk family members or young unmedicated patients with schizophrenia (Caligiuri & Lohr, 1994; Corson, Nopoulos, Andreasen, Heckel, & Arndt, 1999; Gangadhar, Jayakumar, Subbakrishna, Janakiramaiah, & Keshavan, 2004; Keshavan et al., 1998; Woodward et al., 2007).

The greater engagement of right medial frontal cortex in the patients on random relative to sequenced trials, and the absence of a similar difference in the controls, is not likely indicative of cerebral pathology related to procedural learning because neither group showed an association between activation in this region and activation of relevant subcortical structures. This appears to be an extension of the similar increased signal change on random compared to sequenced trials observed in both the patient and control groups in the right precentral gyrus, right precuneus, and three regions of the right inferior parietal lobe, all of which are consis-

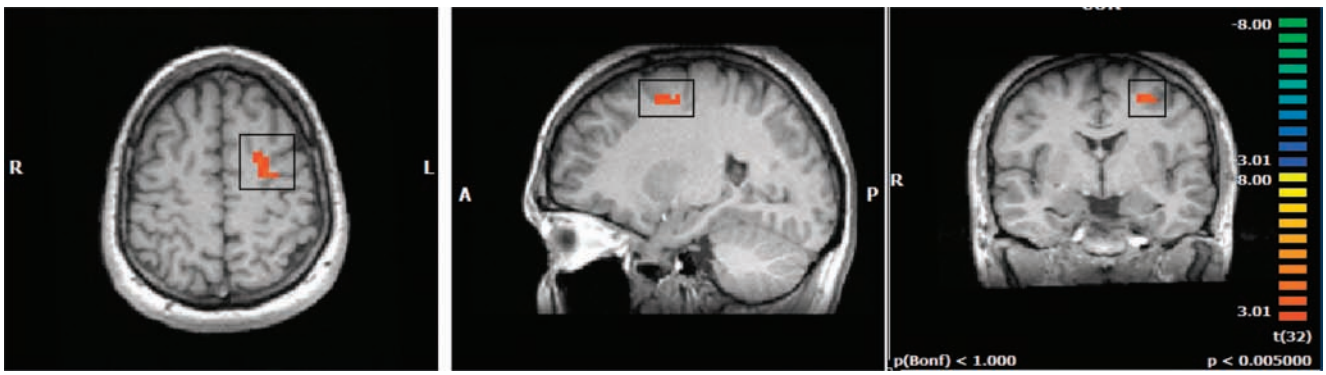

Figure 2. Region of left middle frontal gyrus differentiating between first episode psychosis and HCs on BOLD signal change to SEQ relative to RANrF. *Note:* Details of the activation in left middle frontal gyrus depicted in Table 3. HCs showed more activation of this region on sequenced trials relative to random trials, not apparent in the first episode psychosis sample.

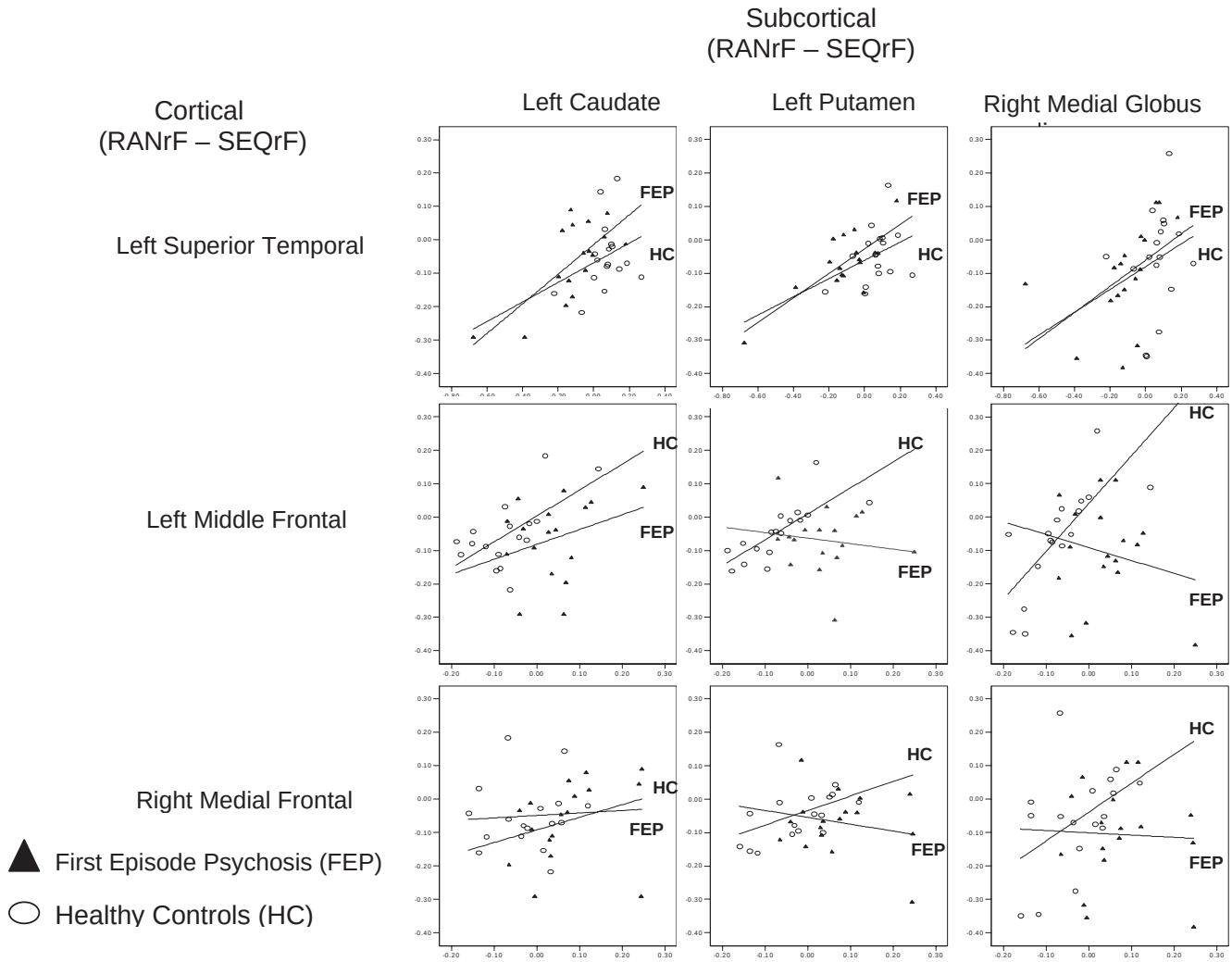

Figure 3. Association between BOLD signal changes on random trials relative to fixation compared to sequenced trials relative to fixation (RANrF-SEQrF) in cortical regions differentiating between groups, and subcortical regions implicated in procedural learning.

tent with expectations that the right hemisphere, particularly the right parietal lobe, would be more engaged under demands for spatial localization in the absence of implicit or explicit memorial cues (e.g., Verleger, Sprenger, Gebauer, Frizmannova, Freidrich, Kraft & Jáskowski, 2009). Although it is unclear why the schizophrenia sample would show additional involvement of the right frontal cortex for spatial localization, the discrepancy is not inconsistent with the postulated absence of right hemisphere pathology in this sample.

The convergence of activation between subcortical structures and the left superior temporal cortex in the patient sample, and the discrepancy between this association and the subcortical-cortical activations in the left middle frontal cortex, are together consistent with a primary cortical dysfunction in the latter. This was most apparent in the associations involving the putamen and the globus pallidus.

In summary, procedural learning and related subcortical and cortical activations were very similar between the two groups, with reliable differentiation between patients and controls in cortical regions with convergent activation of subcortical structures only apparent in a deficient activation of left middle frontal cortex and excess activation of left superior temporal cortex. The absence of evidence of subcortical or right hemisphere pathology contrasts with the bilateral cortical and subcortical anomalies reported in prior fMRI investigations of SRT procedural learning in more chronic medicated samples of patients with schizophrenia (Kumari et al., 2002; Reiss et al., 2006; Zedkova et al., 2006). If the previously documented reductions in subcortical and right cortical activations were related to striato-thalamo-cortical circuit dysfunction caused by neurodevelopmental pathology, then this pathology would be anticipated in the current unmedicated first episode sample. The absence of such pathology suggests that the cerebral dysfunction implicated in prior studies may occur with illness progression or initiation of treatment.

Cerebral alterations related to a degenerative pathology or unspecified effects of ongoing illness (e.g., prolonged substance use, social isolation) cannot be ruled out, but deleterious effects of

antipsychotic medications appear to offer a reasonable explanation because typical antipsychotic medications compromise SRT procedural learning in healthy controls (Kumari et al., 2002) and undermine other procedural learning skills in healthy controls and patients with schizophrenia (Danion et al., 1992; Peretti et al., 1997; Purdon, Woodward, Lindborg, & Stip, 2003; Purdon, Woodward, Mintz, & Labele, 2002; Scherer et al., 2004). Moreover, antipsychotic medications have been linked to an asymmetrical shift toward greater right hemisphere cerebral dysfunction in schizophrenia by investigations of olfactory acuity, hand force persistence, dichotic listening, visual field acuity, and haptic perception (Purdon & Flor-Henry, 2000; Purdon, Woodward, & Flor-Henry, 2001; Seidman et al., 1993; Tomer & Flor-Henry, 1989; Tomer, 1989). These investigations have consistently demonstrated left hemisphere dysfunction in unmedicated or minimally medicated patients with schizophrenia, suggesting deficits not dependent on medication status or degeneration after onset of illness. The diminished activation in the left middle frontal cortex during procedural learning observed in the current sample of unmedicated patients is consistent with this interpretation, and suggests additional regional specificity to the apparent early onset left hemisphere dysfunction that may relate to a neurodevelopmental process, rather than medications or disease progression.

This is the first report of unmedicated patients examined with SRT procedural learning induced BOLD signal changes on fMRI, and the results must be viewed with caution until replication studies are complete and several limitations have been addressed. For example, the groups did not differ in SRT procedural learning, but we cannot be certain that the SOC sequences and open-ended query were sufficient to exclude group differences in the use of explicit recall strategies. The sample sizes reported here are large relative to prior fMRI reports, but they are too small to entirely reject a Type II error explanation of the lack of differences between groups in both SRT procedural learning and subcortical fMRI activations. Given the absence of even a small magnitude numerical difference in SRT procedural learning between the patients and healthy controls, it is unlikely that statistical power limitations can account for the present results. However, replication in a larger sample will be required to confidently conclude the absence of significant SRT procedural learning limitations, basal ganglia pathology, or right cortical dysfunction in unmedicated first episode schizophrenia. Finally, statistical mapping of BOLD signal changes on fMRI entails a very large number of contrast comparisons that will increase the likelihood of a Type I error. This is not relevant to the absence of differences in the subcortical comparisons noted above, and it is less relevant to the predicted group differences in left frontal cortex during procedural learning, but it may have contributed to spurious cortical differences in the left temporal and right frontal regions where unpredicted excess activation was detected in the patient sample.

The present study demonstrated relatively intact procedural learning in schizophrenia, similar to reports using other methods to quantify procedural learning, but discrepant from prior SRT procedural learning investigations of medicated patients. In future studies it would be useful to directly examine the effects of medication on basal ganglia structure and function using both volumetric and functional MRI within a prospective investigation after random assignment of patients to a circumscribed range of typical and atypical antipsychotic medications. This would allow additional coregistration of the SRT procedural learning limitations to cerebral function, facilitating the assessment of associations between cognitive limitations and treatment. It could also begin to offer an indication of the relative merits of various treatments. The prospective investigation could also address the timeline and reversibility of the acquired dysfunction, both particularly important in light of recent reports of significant enlargement of the bilateral caudate in first episode patients after only 3 weeks of neuroleptic treatment (Chua et al., 2008), and a direct correlation between procedural learning and the volume of the presupplementary motor area that may be related to duration of treatment (Exner, Weniger, et al., 2006). Procedural learning is fundamental to human learning and memory, and it may be essential to the perceptual and motor skill learning that provides a foundation for higher cognitive skills, language, emotional recognition, social skills, and intuition (Leiberman, 2000), all of which appear to be implicated in schizophrenia. Delineation of the relative contributions of neurodevelopmental and acquired dysfunction may prove essential to avoiding harm and facilitating rehabilitation.

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