Neural Changes Associated With Relational Learning in Schizophrenia

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Relational learning, which is learning the relationship among items, is impaired in schizophrenia but can be improved with training. This study investigated neural changes with functional magnetic resonance imaging before and after training on a relational learning task in schizophrenia and healthy control subjects. Despite their acquiring similar relational learning performance, the groups exhibited different neural activation patterns before and following training. Controls engaged regions within the relational learning network that included frontal, parietal, and medial temporal lobe, before and following training. Controls also exhibited activation reductions in region and spatial extent with relational learning proficiency, a commonly observed phenomenon in successful learning. In contrast, subjects with schizophrenia displayed no positive activations compared with the control condition before training. After training, subjects with schizophrenia displayed bilateral inferior parietal region activation as predicted. Contrary to hypothesis, hippocampal activation was not observed following training in schizophrenia. These findings suggest that the parietal lobe may be receptive to cognitive training interventions and that successful relational learning may be achieved in schizophrenia through the use of alternative extrahippocampal brain regions.

Key words: fMRI/hippocampus/training/transverse patterning/brain/relational memory

Introduction

Learning and memory processes are particularly impaired in schizophrenia and are predictors of psychosocial function.1,2 Emerging evidence suggests that memory improvement in schizophrenia can be achieved with training or cognitive remediation strategies.3–5 Relational learning is described as learning the relationship among items and is impaired in schizophrenia.6,7 However, when provided with training, subjects with schizophrenia can successfully learn a relational learning paradigm called transverse patterning (TP).8 TP is equivalent to the childhood game “rock, paper, and scissors” that requires one to learn the relationship among 3 items.9 TP depends upon intact medial temporal lobe (MTL) function as illustrated by animal and human studies (ie, rodents,10 primates,11,12 and humans13,14). One functional magnetic resonance imaging (fMRI) study reported impaired performance and abnormal hippocampal and parietal activation during a relational learning task in schizophrenia.7 However, little is known about the neural changes that occur with successful relational learning in schizophrenia.

This study investigated neural changes with fMRI before and following training on the relational learning paradigm TP in schizophrenia and healthy subjects. It is important to note that healthy subjects can achieve at least 80% accuracy on the TP task without training15 but subjects with schizophrenia cannot.8 Achieving this level of accuracy is necessary to ensure that subjects are learning the entire TP problem and not a subset. It was hypothesized that (1) subjects with schizophrenia would not show fMRI MTL and parietal activations during the TP condition pretraining but would following training and (2) control subjects would show fMRI MTL and parietal activations both pretraining and posttraining. This is the first study to report on neural changes associated with relational learning training in subjects with and without schizophrenia.

Method

Subjects

Seventeen outpatients with schizophrenia treated with antipsychotic medication and 17 healthy volunteers participated in this study. The inclusion/exclusion criteria for volunteers with schizophrenia were: (1) diagnosis of
schizophrenia as determined with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), Patient Version (SCID-P16), (2) no current or past neurological condition, (3) no DSM-IV substance abuse or dependence (other than nicotine) in the last 6 months, (4) clinically stable as determined by their treatment psychiatrist, (5) same type and dose antipsychotic for at least 3 months, and (6) right-handed. The inclusion/exclusion criteria for healthy volunteers were: (1) no past or present psychiatric disorder as determined with the Structured Clinical Interview for DSM-IV, Non-Patient Version (SCID-NP16), (2) no first-degree relatives with a diagnosis of a psychotic disorder, (3) no current or past neurological condition, (4) no DSM-IV substance abuse or dependence (other than nicotine) in the last 6 months, and (5) right-handed. Volunteers with schizophrenia were evaluated for their ability to provide informed consent before signing consent documents. All subjects gave written informed consent prior to participation in the study. This study was approved by the University of Maryland and Johns Hopkins University Internal Review Committees.

Course of Events
This study was conducted over 4 sessions. Psychiatric and neuropsychological assessments were conducted during session 1. Session 2 consisted of the first “pretraining” fMRI scan, session 3 consisted of behavioral TP training, and session 4 consisted of the second “posttraining” fMRI scan. Magnetic resonance (MR) scanning sessions took approximately 1 h and were approximately 1 week apart (mean = 7 days, standard deviation = 1) with the training session falling in between (mean = 3 days before second scan, standard deviation = 1). Patients were evaluated for psychopathology with the Brief Psychiatric Rating Scale (BPRS17) and the Scale for the Assessment of Negative Symptoms (SANS18). All subjects completed the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS19) as a measure of general cognitive function. Subjects were monetarily compensated for their time.

Behavioral Task
For the relational learning TP condition, subjects learned the relationship between 3 pairs of overlapping stimuli (eg, A > B, B > C, C > A); and for the nonrelational learning simple discrimination (SD) condition, subjects learned which item in the pair was correct for 3 pairs of nonoverlapping stimuli (eg, D > E, F > G, H > I).

Training
The training procedures are similar to previously described animal and human studies10,15,20 where the 2 conditions, TP and SD, were administered in a stepwise fashion. Subjects completed 6 phases. Phases 1–3 pertained to the SD condition and phases 4–6 pertained to the TP condition. Trials were presented in blocks that contained 16 trials “per pair.” Advancement to the next phase required the subject to score 13 out of 16 correct responses per pair within a block. This criterion was important to ensure subjects were learning the entire problem and not a subset of it. A maximum of 10 blocks per phase was allowed. For phases 1 and 4 which included 1 pair, the maximum number of trials was 160; for phases 2 and 5 which included 2 pairs, the maximum number of trials was 320; and phases 3 and 6 which included 3 pairs, the maximum number of trials was 480. The last phase 6 of TP is considered hippocampal dependent. The computerized task was created with EPRIME software (Psychology Software Tools, Inc, Pittsburg, PA). See figure 1 for illustration.

MR Scanning
MR scanning was conducted on a 3-T Philips Intera with an 8-channel SENSE head coil at the FM Kirby Imaging Center, Kennedy Krieger Institutes, Johns Hopkins Medical Institutes (Philips Medical Systems, Best, The Netherlands). FMRI was acquired with single-shot gradient echo, echo-planar imaging. Volumes were obtained with ascending oblique slices parallel to the hippocampal axis (repetition time = 2.3 s, echo time = 30, flip angle = 70, slice thickness = 2.5, gap = 0.5, slices = 44, and field of view = 240 × 240). Slice thickness and orientation were chosen to optimize the signal obtained from the hippocampus. The imaging protocol consisted of fMRI scans during initial TP learning (ie, pretraining) and following training (posttraining). Due to the nature of the task, TP and SD events must be presented in groups to facilitate learning. Therefore, an event-related design consisting of alternating groups of 12 events of TP and SD was used. A trial started with a presentation of a stimulus pair for 2.5 s, followed by a response opportunity window that was pseudorandomly jittered at 1.5, 2, or 2.5 s where a fixation point was presented and ended with feedback of either a “√” for a correct response, an “X” for incorrect response, or a “?” for no response for 500 ms. Intertrial intervals were pseudorandomly jittered at 1.5, 2, or 2.5 s. Within each run, there were 36 TP tasks and 36 SD control trials, with occurrences of each type counterbalanced in a pseudorandom manner. The pretrained fMRI scan consisted of 4 runs totaling 144 trials per condition. The posttraining fMRI scan consisted of 3 runs totaling 108 trials per condition to allow for diffusion tensor imaging and proton magnetic resonance spectroscopy (1H-MRS) scanning not presented in this paper. Each fMRI time series was approximately 10 minutes long. Subjects were introduced to this task before the scan (during Visit 1) to ensure they understood the task procedures. Different stimuli were used for this introduction session.

Analyses
FMRI analyses were conducted with SPM2 (Wellcome Department of Cognitive Neurology, London, UK,
To allow for T1 equilibrium, the first 4 images (9.2 s) out of 306 were eliminated from analyses. Image preprocessing included correction for motion by coregistration to the first image in each series, correction for differences in slice acquisition times, normalization to a standard Montreal Neurological Institute template, and smoothed by convolution with a Gaussian kernel function (full width at half maximum = 10 mm). Data were analyzed with random effects using SPM2. The contrast [task − control, (TP-SD)] is presented. All within and between group comparisons were quantitatively assessed using dependent and independent t-tests, respectively. Statistical significance was set at \( P < .001 \), cluster extent size > 10. Only correct trials were examined. Due to strong hypothesis regarding hippocampal involvement in relational learning, between group differences for blood oxygen level dependence (BOLD) activation within the whole hippocampus was examined with an region of interest (ROI) mask approach. The hippocampal mask was created with WFU_PickAtlas software toolbox and statistical significance was set at \( P < .005 \). In addition, the BOLD signal change was extracted from hippocampal ROIs (spherical, 5-mm radius) for each group using SPM2.

http://www.fil.ion.ucl.ac.uk/spm/software/spm2). To allow for T1 equilibrium, the first 4 images (9.2 s) out of 306 were eliminated from analyses. Image preprocessing included correction for motion by coregistration to the first image in each series, correction for differences in slice acquisition times, normalization to a standard Montreal Neurological Institute template, and smoothed by convolution with a Gaussian kernel function (full width at half maximum = 10 mm). Data were analyzed with random effects using SPM2. The contrast [task − control, (TP-SD)] is presented. All within and between group comparisons were quantitatively assessed using dependent and independent t-tests, respectively. Statistical significance was set at \( P < .001 \), cluster extent size > 10. Only correct trials were examined. Due to strong hypothesis regarding hippocampal involvement in relational learning, between group differences for blood oxygen level dependence (BOLD) activation within the whole hippocampus was examined with an region of interest (ROI) mask approach. The hippocampal mask was created with WFU_PickAtlas software toolbox and statistical significance was set at \( P < .005 \). In addition, the BOLD signal change was extracted from hippocampal ROIs (spherical, 5-mm radius) for each group using SPM2.

Fig. 1. Illustration of Task Conditions and Training. For a trial, one pair of stimuli is presented. The subject’s goal is to learn the correct item in each pair. A “+” sign indicates the correct choice and a “−” sign indicates an incorrect choice. The transverse patterning (TP) condition requires relational learning, whereby an item is correct or incorrect depending on the item it is paired with. The SD condition does not require relational learning. Training consisted of 6 phases, 1–3 for the SD condition and 4–6 for the TP condition. Trials were presented in blocks that contained 16 trials per pair. Advancement to the next phase required the subject to score 13 out of 16 correct responses per pair within a block. Phases 3 and 6 depict the full SD and TP task that were administered during the functional magnetic resonance imaging sessions.

Results

Subject demographic and clinical characteristics are provided in table 1. As expected, volunteers with schizophrenia had fewer years of education (\( t(32) = 2.59, P < .05 \)) and lower RBANS scores (\( t(32) = 2.33, P < .01 \)) when compared with healthy controls. Covarying for these variables made no difference in the results presented in the following sections. There were no significant differences in age, gender, or ethnicity between groups (all \( P’s > .05 \)).

Behavior during fMRI

Two 2 (group: schizophrenia, control) \( \times 2 \) (fMRI session: pretraining, posttraining) ANOVAs with repeated measures on fMRI session were conducted for TP and SD accuracies. There were no statistically significant interactions or group effects. There were significant main effects for fMRI session (TP: \( F(1,32) = 46.7, P < .05 \); SD: \( F(1,32) = 6.7, P < .05 \)) indicating TP and SD performance improved from pretraining to posttraining averaged across groups. Simple effects analyses (Bonferroni-corrected, alpha (significance) set to \( P < .0125 \)) indicated that both groups significantly improved on the TP task with training (controls: \( t(16) = 3.5, P < .01 \), schizophrenia: \( t(16) = 7.1, P < .01 \)), but only the schizophrenia group approached trend significance for improved performance on the SD task with training (schizophrenia: \( t(16) = 2.76, P = .014 \)). Mean accuracy (standard deviation) during fMRI 1 for TP was schizophrenia: 63.2 (16.3), controls: 69.3 (18.4) and for SD was schizophrenia: 90.3 (14.7), controls: 95.4 (4.9). Means (standard deviations); during fMRI 2 for TP were schizophrenia: 82.0 (17.5), controls: 83.4 (18.3) and for SD were schizophrenia: 97.8 (4.8), controls: 96.5 (6.6).
Whole-Brain Analyses between Groups. During initial TP learning, greater activation in right inferior frontal, right precentral gyrus, right inferior parietal, and left middle temporal regions was observed in the control compared with the schizophrenia group. Following training, greater activation in the right middle cingulate, right temporal, and left parietal regions was observed in the control compared with the schizophrenia group.

Hippocampal Mask ROI Analyses. During initial TP learning, control compared with schizophrenia subjects revealed greater activation in the left posterior hippocampus. Control subjects exhibited a positive BOLD signal change, whereas schizophrenia subjects exhibited a negative BOLD signal change. Following training, control compared with schizophrenia subjects revealed greater activation in the right anterior hippocampus. Control subjects exhibited a positive BOLD signal change, whereas schizophrenia subjects exhibited a negative BOLD signal change.

Discussion

This study investigated the neural changes that occurred before and after training on the TP relational learning task in subjects with and without schizophrenia. Subjects with schizophrenia were not significantly different from control subjects with respect to relational learning performance before and following training. Despite similar relational learning performance, the groups exhibited different fMRI patterns before and after training. This study provides new evidence that successful relational learning in schizophrenia is accomplished through neural changes in brain regions different from that of healthy subjects. Importantly, subjects with schizophrenia accomplish relational learning through extrahippocampal brain regions.

Different profiles of regional activation for subjects with and without schizophrenia in the pretraining and posttraining TP-SD contrast indicate different neural solutions to relational learning. The TP-SD contrast strongly reflects relational learning processes because those processes involved in perception, attention, discrimination, and motor response have been removed (ie, activations in SD). Healthy subjects engaged frontal, parietal, and medial temporal regions, which are part of a neural network commonly associated with relational learning. Activation in these regions was observed both pretraining and posttraining, but there were reductions in the spatial extent but enhanced regional specificity with learning. With respect to the frontal and parietal regions, multiple regions within these areas were engaged pretraining and these were reduced to one region in the right inferior frontal and one region in the left parietal (precuneus) posttraining. Such neural changes from a distributed to focal network are consistently reported across different types of learning. This likely reflects neural...
changes associated with greater task precision and efficiency. With respect to the hippocampus, ROI analyses revealed that the left posterior hippocampus was engaged during early relational learning or pretraining, whereas the right anterior hippocampus was engaged during retrieval of relational information or posttraining. This is consistent with studies that report the posterior hippocampus involvement in encoding of relational information and the anterior hippocampus involvement in the flexible retrieval of relational information. The distinction between posterior and anterior hippocampal activation could also be attributed to a different mnemonic process used pretraining vs posttraining. According to Giovanello et al., the posterior hippocampus is involved in “reinstatement of items” or “establishing a fixed perceptual representation,” processes that could

### Table 2. Whole-Brain Analysis Results

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Cluster Size (Voxel Number)</th>
<th>Z Score</th>
<th>Montreal Neurological Institute</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pretraining (Task - Control)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive activations</td>
<td>Right precentral gyrus</td>
<td>72</td>
<td>4.56</td>
</tr>
<tr>
<td></td>
<td>Left posterior para/hippocampus</td>
<td>34</td>
<td>3.55</td>
</tr>
<tr>
<td>Negative activations</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Schizophrenia group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive activations</td>
<td>Right inferior frontal gyrus</td>
<td>114</td>
<td>4.14</td>
</tr>
<tr>
<td>Negative activations</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control vs schizophrenia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive activations</td>
<td>Right inferior frontal gyrus</td>
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<td>Negative activations</td>
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<td></td>
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</tr>
<tr>
<td><strong>Posttraining (Task - Control)</strong></td>
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<td></td>
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</tr>
<tr>
<td><strong>Control group</strong></td>
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</tr>
<tr>
<td>Positive activations</td>
<td>Right inferior frontal</td>
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<td>3.72</td>
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<tr>
<td></td>
<td>Right middle cingulate</td>
<td>10</td>
<td>3.38</td>
</tr>
<tr>
<td></td>
<td>Left precuneus</td>
<td>33</td>
<td>3.77</td>
</tr>
<tr>
<td></td>
<td>Right fusiform</td>
<td>32</td>
<td>4.12</td>
</tr>
<tr>
<td>Negative activations</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Schizophrenia group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive activations</td>
<td>Right inferior parietal</td>
<td>44</td>
<td>3.83</td>
</tr>
<tr>
<td></td>
<td>Left inferior parietal</td>
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<td>3.39</td>
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<tr>
<td>Negative activations</td>
<td>Left superior temporal</td>
<td>85</td>
<td>4.08</td>
</tr>
<tr>
<td></td>
<td>Left middle temporal</td>
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<td>3.56</td>
</tr>
<tr>
<td></td>
<td>Left superior occipital</td>
<td>14</td>
<td>4.08</td>
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<tr>
<td><strong>Control vs schizophrenia</strong></td>
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<tr>
<td>Positive activations</td>
<td>Right middle cingulate</td>
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<td>Left precuneus</td>
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<td>Right inferior temporal gyrus</td>
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<td>3.48</td>
</tr>
<tr>
<td>Negative activations</td>
<td>None</td>
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</table>
occur more often during pretraining, whereas the ante-
rior hippocampus is involved in flexible retrieval of rela-
tional information which occurs more often posttraining 
after the relationship among the items has been success-
fully learned. The shift from the left to the right hemi-
sphere may indicate that subjects used a linguistic 
strategy initially but then used a visual-spatial strategy 
once relational learning became proficient.

Unlike controls, subjects with schizophrenia did not 
follow the normal pattern of engaging a distributed net-
work pretraining that narrowed to a smaller number of 
regions posttraining. This is consistent with previous 
studies showing increased activation following cognitive 
training in schizophrenia.\textsuperscript{5,33} Subjects with schizophrenia 
exhibited no positive activations pretraining but did 
exhibit a negative activation in the right inferior frontal 
region. This negative activation may reflect atypical 
frontal engagement during the SD condition. Inappro-
priate frontal activation is observed in persons with 
schizophrenia.\textsuperscript{34}

By posttraining, subjects with schizophrenia exhibited 
positive activations in bilateral inferior parietal regions, 
a part of the relational learning network. Inferior parietal 
activation was also observed in healthy subjects but during 
pretraining. It is possible that TP training resulted in 
normalized inferior parietal activation in subjects with 
schizophrenia. Deficits in inferior parietal lobe function 
are reported in schizophrenia,\textsuperscript{35} but these results suggest 
that the inferior parietal lobe may be sensitive to cogni-
tive training strategies in schizophrenia. Negative activa-
tions in lateral temporal and medial occipital regions 
were also observed posttraining, which may reflect 
greater engagement in the SD control condition. As 
expected there was no MTL activation pretraining.

Contrary to hypothesis, hippocampal activation was 
not observed posttraining and did not “normalize” fol-
lowing training. This suggests that successful relational 
learning can be achieved through alternative brain net-
works that do not encompass the hippocampus. This 
is consistent with a case study reporting an amnesic with 

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Fig.2.png}
\caption{Different Hippocampal Responses Before and After Relational Learning Training in Control and Schizophrenia Subjects. A. Before training: Left posterior hippocampal activation difference between control and schizophrenia groups (top) and percent signal change per group (bottom). Statistical threshold refers to voxel-based significance set at $P < .005$. B. After training: Right anterior hippocampal activation difference between control and schizophrenia groups (top) and percent signal change per group (bottom). Statistical threshold refers to voxel-based significance set at $P < .005$.}
\end{figure}
extensive bilateral hippocampal damage who successfully learned TP problems that were based on semantic knowledge. He was successful at solving TP problems if he relied on known relations based on semantic knowledge and did not need to establish new relations among items. It is plausible that subjects with schizophrenia accomplished relational learning through the use of extrahippocampal brain regions. This seems likely because hippocampal abnormalities figure prominently in the pathophysiology of schizophrenia, and in a previous fMRI study, the hippocampus was not activated during a relational learning task and displayed a negative signal change similar to this study.

The fMRI activation differences between controls and persons with schizophrenia may reflect different cognitive strategies. One strategy is based on learning the relationship among the items (i.e., A beats B, B beats C, and C beats A), which is thought to be the predominant strategy for successful TP learning. A second strategy is learning the 6 possible configurations (i.e., the winner positioned left or right in the pair) of the stimuli associated with winning. This reduces the TP relational task to a SD task. Following the completion of the study, subjects were asked how they solved the task. Both groups reported solving the TP problem through learning the relationship among the items and not by memorizing the “winner” in each of the 6 possible pairs. Based on this anecdotal evidence, it appears that subjects with schizophrenia did not rely on strategies different from controls for successful relational learning.

There are some study limitations worth mentioning. First, the effect of antipsychotic medication on neural patterns in schizophrenia is not known. It is possible that altered brain activation observed in this study is due to a medication effect. Future studies investigating neural changes during relational learning in subjects with schizophrenia off antipsychotic medications are necessary. Second, it is possible that the neural patterns in schizophrenia would normalize with additional extensive training beyond what this study provided. Future studies incorporating multiple training sessions over several weeks are necessary to determine whether this is the case.

It is very difficult to pinpoint the roots of altered neural patterns in schizophrenia. But the dynamic neural interactions between presynaptic and postsynaptic neurons that characterize learning may be disrupted by GABA-glutamate dysfunctions. The extensive literature documenting a crucial role for glutamatergic neurotransmission in learning may provide clues regarding defective in schizophrenia. N-methyl-d-aspartate receptor hypofunction may critically diminish long-term potentiation and inhibitory–excitatory cooperation in the neocortex. Compromised structural connections between brain regions could also play a role in the altered neural patterns observed in this study. Future studies using multiple imaging methods may provide a clear picture of this fundamental component and help resolve neural alterations in schizophrenia.

This is the first study to investigate brain changes with successful relational learning in schizophrenia using training. These findings provide important implications for schizophrenia: (1) the parietal lobe may be receptive to cognitive training and (2) successful relational learning of a translational “hippocampal-dependent” task may be achieved through the use of alternative extrahippocampal brain regions. In summary, this study reveals that subjects with schizophrenia have neural changes with learning but in different brain circuits than healthy controls. With training intervention, some brain regions may normalize (e.g., parietal), whereas others (e.g., hippocampus) do not.

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