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Computerized Cognitive Training Restores Neural Activity within the Reality Monitoring Network in Schizophrenia

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SUMMARY

Schizophrenia patients suffer from severe cognitive deficits, such as impaired reality monitoring. Reality monitoring is the ability to distinguish the source of internal experiences from outside reality. During reality monitoring tasks, schizophrenia patients make errors identifying “I made it up” items, and even during accurate performance, they show abnormally low activation of the medial prefrontal cortex (mPFC), a region that supports self-referential cognition. We administered 80 hr of computerized training of cognitive processes to schizophrenia patients and found improvement in reality monitoring that correlated with increased mPFC activity. In contrast, patients in a computer games control condition did not show any behavioral or neural improvements. Notably, recovery in mPFC activity after training was associated with improved social functioning 6 months later. These findings demonstrate that a serious behavioral deficit in schizophrenia, and its underlying neural dysfunction, can be improved by well-designed computerized cognitive training, resulting in better quality of life.

INTRODUCTION

A long-debated and critical question in schizophrenia and other neuropsychiatric illnesses is whether the underlying neural impairments of the disorder are immutable fixed, or whether they can respond in a significant and enduring manner to targeted behavioral interventions. Here, we demonstrate that intensive neuroscience-informed cognitive training can improve brain function in patients who have been ill for decades. Specifically, we show that it can improve a complex and clinically meaningful “reality monitoring” process defined as the ability to distinguish the source of internal experiences (self-generated information) from outside reality (external information) (Bentall et al., 1991; Johnson et al., 1993; Keefe et al., 1999; Morrison and Haddock, 1997; Vinogradov et al., 1997, 2008). Furthermore, we demonstrate that training-induced enhancement of neural activation patterns associated with reality monitoring predict subsequent improvement in longer-term social functioning. This study also addresses the fundamental issue of whether “brain training” improves cognitive functions beyond the trained tasks (Owen et al., 2010).

Schizophrenia is a serious and debilitating psychiatric illness that affects 51 million people worldwide. Affected individuals experience a range of disturbing clinical symptoms indicating a break with reality—such as hallucinations and delusions—as well as a range of neurocognitive and social cognitive deficits (Cirillo and Seidman, 2003; Heinrichs and Zakzanis, 1998). Prominent among these deficits are impairments in memory, executive function, and in the assessment of social cues such as facial emotion (Chan et al., 2010; Glahn et al., 2000; Silver et al., 2007). Pharmacologic treatment of schizophrenia targets symptom reduction, but the neurocognitive and social cognitive impairments, which are not improved by current medications, are more predictive of poor functional outcome than are the clinical symptoms of hallucinations and delusions (Evans et al., 2004; Green et al., 2000). Despite an understanding of the strong association between cognitive impairment and long-term disability in patients, the treatment of schizophrenia is at a stalemate (Carter and Barch, 2007; Marder and Fenton, 2004). New cognitive-enhancing medications studied thus far have been disappointing, and conventional psychotherapeutic and psychosocial rehabilitation approaches have been of limited benefit, likely due to the cognitive limitations of the illness (Green et al., 2008; Pilling et al., 2002; Smith et al., 2010).

Informed by the past two decades of systems neuroscience research into the learning mechanisms that drive sustained plastic changes in the cortex (Buonomano and Merzenich, 1998; Jenkins et al., 1990; Karni and Sagi, 1991; Merzenich et al., 1990), we predicted that—in order to improve higher order cognitive functions in human neuropsychiatric illness—computerized training must be designed to intensively target impairments in lower-level perceptual processing as well as working memory and executive operations (Adcock et al., 2009; Fisher et al., 2009; Mahncke et al., 2006; Vinogradov et al., 2012). In other words, training must initially target lower-level processes in order to increase the accuracy, the temporal and
data, with general cognitive abilities contributing to task perfor-
(Fisher et al., 2008). The overall picture is one of reduced effi-
memory, executive function, and basic social cognition that is
are associated with a pattern of impairments in attention,
2008). Further, in schizophrenia, these reality monitoring deficits
they show relative underactivation of mPFC (Vinogradov et al.,
tasking experiments, and even during accurate task performance,
"other" condition).
graphs of the same building taken by another person (the
graphical "self" condition) versus when they viewed photo-
activation was greater when subjects viewed photo-
effects to working memory and executive functions, ultimately
spatial resolution, and the signal strength of auditory and visual
inputs to working memory and executive functions, ultimately
increasing the efficiency of more complex, higher-level cognitive
processes in an enduring manner (Vinogradov et al., 2012).
Specifically, we predicted that deficits in a type of source memory
known as reality monitoring—the ability to distinguish the source
of stimuli that have been internally generated from those that
have been experienced externally (to separate “inner world”
from “outer reality”)—would respond to intensive training of
component aspects of auditory/verbal, visual, and social cogni-
tive processes in patients with schizophrenia. We also predicted
that improved reality monitoring in patients would be associated
with more normal neural activation patterns in the medial pre-
frontal cortex. Finally, we hypothesized that training-induced
increases in prefrontal activation patterns would predict im-
poved real world social functioning 6 months later.

In healthy individuals, performance on simple reality moni-
toring experiments that assess how well someone can distin-
guish the source of self-generated word items from externally
presented word items (“I remember that I made that word up”
versus “I remember that you showed it to me”) is strongly related
to the person’s ability to recognize faces and to identify facial
and vocal emotion (Fisher et al., 2008). It is also associated
with activation of the medial prefrontal cortex (mPFC), a critical
node in the neural network that supports the processing of social
cognitive information (Frith and Frith, 1999; Gilbert et al., 2007;
Heberlein et al., 2008; Hooker et al., 2011; Mattavelli et al.,
2011; Northoff et al., 2006; Phan et al., 2002; Sabatinelli et al.,
2011; Vinogradov et al., 2006, 2008). In other words, the same
neural systems that participate in distinguishing “inner world”
from “outside world” also support the representation of “self”
and “other”; indeed, the anterior rostral mPFC is particularly
implicated in tagging information as being relevant to the “self”
(Amodio and Frith, 2006; Ochsner et al., 2004, 2005; Vinogradov
et al., 2006, 2008). For example, Cabeza et al. (2004) found that
mPFC activation was greater when subjects viewed photographs of a building that they themselves had taken (the autobiographical “self” condition) versus when they viewed photographs of the same building taken by another person (the “other” condition).

Not surprisingly, individuals with schizophrenia have particular
difficulty recognizing “I made it up” items during reality moni-
toring experiments, and even during accurate task performance,
they show relative underactivation of mPFC (Vinogradov et al.,
2008). Further, in schizophrenia, these reality monitoring deficits
are associated with a pattern of impairments in attention,
memory, executive function, and basic social cognition that is
quite different from what is observed in healthy individuals
(Fisher et al., 2008). The overall picture is one of reduced effi-
ciency, lower accuracy, and less reliability when individuals with schizophrenia are required to distinguish between “inner world” and “outside reality” and/or to process socially relevant data, with general cognitive abilities contributing to task perfor-
mance (Fisher et al., 2008). The ongoing real-world conse-
quences of this kind of metacognitive disability are potentially
quite profound, and could include a disturbed sense of agency,
decreased insight, and abnormal social behavior. These data
also suggest, however, that targeted improvement of basic
attention, memory, executive, and social cognitive opera-
tions could potentially benefit higher-level reality monitoring in
schizophrenia.

The present study, therefore, addressed a series of questions
fundamental to neuroscience-informed cognitive training and to
a “neural systems” approach to the treatment of schizophrenia:
(1) Even after years of illness, can intensive computerized
training of component perceptual, working memory, executive,
and social cognitive processes in schizophrenia patients lead
to sustained improvements in reality monitoring? (2) Is training-
induced improvement in reality monitoring performance accom-
ppanied by an increase in mPFC activation patterns? Do training-
induced increases in mPFC activity correlate with improved task
performance? (3) Is a training-induced increase in mPFC activity
associated with long-term improvements in real world social
functioning?

Improvement in reality monitoring in patients with schizo-
phrenia was tested via pre- and posttraining assessments of
behavioral performance and functional magnetic resonance
imaging (fMRI) activation patterns during a reality monitoring
task. We enrolled 31 schizophrenia (SZ) patients and 15 healthy
comparison (HC) subjects in a baseline fMRI reality monitoring
experiment (Table 1 and Figure 1A). Next, SZ subjects were
randomly assigned to either an active training (SZ-AT) or a control
condition computer games (SZ-CG) intervention (Table 2). The
SZ-AT group participated in 80 hr of intensive computerized
cognitive training, while the SZ-CG group participated in 80 hr
of a rotating series of commercial computer games. Both SZ
groups participated for approximately 5 hr/week over 16 weeks
in the laboratory. The SZ-AT subjects were trained on basic audi-
tory/verbal, visual, facial emotion recognition, and theory of mind
processes that were embedded within increasingly more com-
plex working memory exercises, with the objective of enhancing
the neural systems that support the fidelity and reliability of audi-
tory, visual, verbal, and social cognitive working memory (Delahunt
et al., 2008; Fisher et al., 2009; Mahncke et al., 2006). After
16 weeks, 15 SZ-AT, 14 SZ-CG, and 12 HC subjects participated
in a second fMRI reality monitoring experiment. Six months later,
13 SZ-AT and 12 SZ-CG subjects agreed to return to the labora-
tory for a follow-up visit and re-assessment of their clinical and
functional status.

Each fMRI session consisted of a word-generation phase
performed outside the scanner prior to scanning, and a reality
monitoring task performed during scanning (Figure 1A). In the
word-generation phase, subjects were presented with a list of

<table>
<thead>
<tr>
<th>Table 1. Demographics (Mean, SD) of HC and SZ Subjects</th>
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<tr>
<td><strong>HC (n = 16)</strong></td>
</tr>
<tr>
<td>Age 45 (11.6)</td>
</tr>
<tr>
<td>Gender     M, F</td>
</tr>
<tr>
<td>Education (years)      14 (1.35)</td>
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<tr>
<td>IQ          115 (11.45)</td>
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*There was a statistically significant difference in IQ between HC and SZ subjects at baseline (t = 2.01, p = 0.052); therefore, we used partial corre-
lations for all behavioral training effects in order to control for any baseline
differences in age, education, and IQ.
semantically constrained sentences with the structure “noun-verb-noun.” The final noun was either presented by the experimenter (e.g., The sailor sailed the sea), or left blank for subjects to generate themselves and then recorded by the research assistant (e.g., The rabbit ate the __). During the reality monitoring task in the scanner approximately 45 min later, subjects were visually presented with noun pairs from the sentence list (e.g., rabbit-carrot) and had to indicate whether the second
word was previously self-generated (“I made it up”) or externally presented (“You showed it to me”) by making a button-press with their right dominant hand (Vinogradov et al., 2008). In healthy subjects, identification of the source of self-generated word items is associated with greater fMRI activity in the dorsal rostral portion of the anterior cingulate cortex (ACC) and mPFC, relative to identification of externally presented items (Vinogradov et al., 2006, 2008). In contrast, patients with schizophrenia are known to be significantly less accurate in the identification of the source of self-generated items (but not externally presented word items), and exhibit no fMRI activity in mPFC and ACC during this reality monitoring task (Vinogradov et al., 2008). We examined both behavioral performance and fMRI neural activity in our subject groups, at baseline and after 16 weeks, contrasting correct trials for identification of self-generated word items with correct trials for externally presented word items.

RESULTS

Behavioral and fMRI Findings Prior to Intervention

To examine performance on the reality monitoring task at baseline, accuracy scores were submitted to a repeated-measures analysis of variance (ANOVA) with group (HC, SZ) as a between-subject factor and condition (self-generated, externally presented) as a within-subject factor. At baseline, consistent with our previous findings (Vinogradov et al., 1997, 2008), we found a significant group by condition interaction (F(2,44) = 3.32, p = 0.05), driven by the HC subjects who identified significantly more self-generated items than SZ subjects (F(1,45) = 6.78, p = 0.01), but not more externally presented items (F(1,45) = 0.71, p = 0.40) (Figure 1B). In order to correct for any response bias on the reality monitoring task, we utilized signal detection theoretic analyses to compute a d-prime score for overall reality monitoring source memory performance. Signal detection theoretic analysis confirmed that HC subjects performed significantly better than SZ subjects during overall source memory identification of word items (F(1,45) = 4.19, p = 0.047) (Figure 1B). The effect size of the overall source memory accuracy difference between HC and SZ subjects at baseline was 0.65. After baseline testing, the SZ subjects were randomly assigned to either active training (SZ-AT) or to computer games (SZ-CG). An ANOVA with the three groups at baseline (HC, SZ-CG, and SZ-AT subjects) revealed a significant main effect of group in d-prime scores: HC subjects were more accurate than SZ-CG and SZ-AT subjects (F(2,44) = 3.57, p = 0.037), but there was no accuracy difference in d-prime scores between SZ-CG and SZ-AT subjects (F(1,29) = 2.17, p = 0.15), indicating that the two patient groups showed similar task performance at baseline.

To examine mPFC fMRI activity during reality monitoring, we defined an a priori 20 mm (radius) spherical region of interest (ROI) according to Cabeza et al. (2004) locus of mPFC activity, for self-referential memory reported in a sample of psychiatrically healthy subjects, centered on –4, 52, 8 Talairach coordinates. We first conducted multiple one-sample t tests within each group (HC, SZ-CG, and SZ-AT) at baseline to assess reality monitoring activity (i.e., activity for correctly identified self-generated items versus activity for correctly identified externally presented items) on a voxel-by-voxel basis, using the spherical a priori mPFC ROI as an explicit mask. Multiple comparison corrections were then performed within the mPFC ROI, with the FWE correction of p < 0.05 and with a cluster extent of 0, using the small volume correction (SVC) implemented in SPM2. Results from these one-sample t tests revealed that the HC group was the only group at baseline to activate voxels that survived this FWE correction (p < 0.05) within the mPFC ROI (Figure 1C). Neither the SZ-AT nor SZ-CG groups activated any voxels that survived the FWE correction (p < 0.05) within the mPFC ROI at baseline. Next, for all group correlations and for all between-group ANOVAs, mean beta weights from the self-generated versus externally presented comparison were calculated across all voxels within the a priori spherical mPFC ROI for each group. These mean beta weights were submitted to a one-way ANOVA in SPSS to test for differences between the HC, SZ-CG, and SZ-AT subject groups. The ANOVA between HC, SZ-CG, and SZ-AT subject groups at baseline revealed a significant group effect in mPFC activity for self-generated minus externally presented items (F(2,43) = 7.52, p = 0.002). This group effect at baseline was driven by the HC subjects, who revealed significantly more mPFC activity for self-generated items than externally presented items when compared to the SZ-CG subjects (F(1,28) = 12.75, p = 0.001) and when compared

| Table 2. Medication Profiles of SZ-AT Patients and SZ-CG Patients |
|---------------------------------|----------------|
|                                | SZ-AT (n = 16) | SZ-CG (n = 15) |
| Antipsychotic Medication       |                |                |
| First generation, n            | 0              | 2              |
| Second generation, n           | 11             | 12             |
| Multiple, n                    | 1              | 0              |
| No antipsychotic, n            | 4              | 1              |
| Other Psychiatric Medication   |                |                |
| Antidepressants or mood        | 9              | 5              |
| Benzodiazepines, n             | 4              | 6              |
| Anticholinergics, n            | 2              | 3              |
| Mean Chlorpromazine Equivalents, Mean (SD) | 478 (380) | 419 (453) |
| Mean Cogentin Equivalents, Mean (SD) | 0.73 (0.82) | 1.35 (2.95) | 0.63 | 0.45 |
to the SZ-AT subjects (F(1,29) = 11.08, p = 0.002). There was no significant difference in mPFC activity between SZ-CG and SZ-AT subjects at baseline (F(1,29) = 0.30, p = 0.35). Next, these mean beta weights from the self-generated versus externally presented comparison that were extracted from the a priori spherical mPFC ROI for each group at baseline were correlated with behavioral performance for each group at baseline. Interestingly, only in HC subjects was mPFC signal level within the a priori ROI significantly correlated with accurate overall source memory (r = 0.59, p = 0.02) (Figures 1D and 1E). This correlation was not significant in the SZ-CG subjects (r = −0.18, p = 0.53) or in the SZ-AT subjects (r = 0.25, p = 0.36) at baseline. These data are consistent with the role of mPFC as a critical node in the neural network that supports a range of self-referential processes (Northoff et al., 2006; Ochsner et al., 2004, 2005; Vinogradov et al., 2006), and indicate that schizophrenia patients do not show normal recruitment of this network during a reality monitoring task.

Behavioral Performance Changes Due to Intervention

After 16 weeks in which SZ patients participated in either 80 hr of cognitive training or a rotating series of commercial computer games, subjects returned for a second fMRI reality monitoring experiment. A repeated-measures ANOVA revealed a significant group-by-session interaction in d-prime scores for overall source memory identification of word items (F(2,39) = 4.82, p = 0.013). Specifically, there was a significant group-by-session effect for self-generated word items (F(2,39) = 4.37, p = 0.02) but not for externally presented word items (F(2,39) = 2.34, p = 0.11) (Figures 2A and 2B). The SZ-AT subjects, when compared to the SZ-CG subjects, identified the source of significantly more word items overall at 16 weeks compared to baseline (F(1,28) = 6.98, p = 0.01) and also specifically identified more self-generated items (F(1,28) = 5.87, p = 0.02), with a trend effect for externally presented items (F(1,28) = 3.64, p = 0.07). The SZ-AT subjects, when compared to the HC subjects, identified the source of more word items overall at 16 weeks compared to baseline (F(1,26) = 4.42, p = 0.045), identifying more self-generated (F(1,26) = 5.89, p = 0.02) but not more externally presented items (F(1,26) = 0.97, p = 0.33). There were no differences between sessions for HC or SZ-CG subjects on overall source-memory accuracy (F(1,24) = 0.19, p = 0.67), on self-generated items (F(1,24) = 0.04, p = 0.84) or on externally presented items (F(1,24) = 1.79, p = 0.19). After cognitive training compared to baseline, within-group paired t tests confirmed that SZ-AT subjects identified the overall source of significantly more word items (t(15) = 2.53, p = 0.02), significantly more self-generated items (t(15) = 2.3, p = 0.04), and marginally more externally presented items (t(15) = 2.03, p = 0.06). A comparison of the change in overall source-memory accuracy from baseline to 16 weeks revealed a large effect size of 0.86 in SZ-AT versus SZ-CG subjects, and a medium effect size of 0.61 in SZ-AT versus HC subjects. In contrast, neither HC nor SZ-CG subjects showed significant improvement in overall source memory accuracy at 16 weeks compared to baseline (HC: t(11) = 0.23, p = 0.82; SZ-CG: t(13) = 1.11, p = 0.29). These results indicate that improvement in reality monitoring performance was specific to schizophrenia patients who engaged in 16 weeks of computerized cognitive training.

Brain Imaging Changes Due to Intervention

We performed one-way within-subject ANOVAs to compare reality monitoring activity (i.e., activity for correctly identified self-generated items versus activity for correctly identified externally presented items) on a voxel-by-voxel basis before and after intervention within each group, using the spherical a priori mPFC ROI as an explicit mask. Multiple comparison corrections were then performed within the mPFC ROI with the FWE correction of p < 0.05 and with a cluster extent of 0, using the SVC implemented in SPM2. Results from the one-way within-subject ANOVAs revealed that only the SZ-AT group showed increased mPFC activation during reality monitoring that survived the FWE correction (p < 0.05) at 16 weeks versus baseline (Figure 2C). Next, in order to investigate between-group differences at 16 weeks versus baseline, mean beta weights from the self-generated versus externally presented comparison were extracted across all the voxels within the a priori spherical mPFC ROI for each group and for each session (i.e., at baseline, and at 16 weeks). These mean beta weights were submitted to a repeated-measures ANOVA in SPSS to test for differences between the HC, SZ-CG, and SZ-AT groups in mPFC signal change from baseline to 16 weeks. There was a significant group-by-session interaction in mPFC reality monitoring activity (F(2,38) = 3.49, p = 0.04). This group-by-session effect was driven by the SZ-AT subjects, who had significantly more mPFC signal after the intervention than the SZ-CG subjects (F(1,27) = 4.07, p = 0.05) than the HC subjects (F(1,25) = 4.48, p = 0.04). There were no differences between sessions for HC or SZ-CG subjects in mPFC signal for the self-generated item minus externally presented item comparison (F(1,24) = 0.01, p = 0.91).

Next, these mPFC mean beta weights from the self-generated versus externally presented comparison that were extracted across the a priori spherical mPFC ROI for each group at 16 weeks were correlated with behavioral performance for each group at 16 weeks. Importantly, in the SZ-AT subjects, mPFC signal within the a priori ROI after training was correlated with task accuracy after training (r = 0.53, p = 0.04) (Figures 2D and 2E), similar to the correlation we observed in HC subjects at baseline. These results indicate that, after 16 weeks of intensive training of component cognitive processes, the SZ-AT subjects began to “normalize” their brain-behavior associations during performance of an untrained higher-order reality monitoring task such that they more closely resembled healthy subjects. These brain-behavior associations were not observed in the SZ-CG subjects after 16 weeks of computer games (r = 0.12, p = 0.68).

Association of Reality Monitoring Task Performance and mPFC Activation Levels with Neuropsychological Measures after Cognitive Training

The effects of this form of cognitive training on standard neuropsychological outcome measures in a larger sample of schizophrenia subjects have been previously reported by us (Sacks et al., 2012; Fisher et al., 2009, 2010). In brief, this form of intensive computerized cognitive training drives significant improvements in processing speed, verbal learning and memory, and general cognition in patients with schizophrenia. Here, we describe the associations we observed after training between...
Figure 2. Cognitive Training Effects: Performance and Brain Activation Differences at 16 Weeks among Active Training SZ-AT Subjects, SZ-CG Subjects, and HC Subjects

(A and B) Mean accuracy averaged across three runs for self-generated and externally presented item identification, d-prime scores, and mean mPFC signal are illustrated. Repeated-measures ANOVAs reveal group differences at 16 weeks compared to baseline in (A) self-generated item accuracy, but not externally presented item accuracy, and (B) D-prime scores for overall source memory identification of word items, as well as in mPFC reality monitoring signal averaged across all voxels within the a priori spherical ROI.

(C) Reality monitoring activity in mPFC across 15 SZ-AT subjects after cognitive training compared to baseline within the a priori mPFC ROI. See also Figure S2 and Table S2 for the whole brain analyses of reality monitoring mPFC activity at 16 weeks versus baseline in each group, across (A) 15 SZ-AT, (B) 14 SZ-CG, and (C) 12 HC subjects.

(D and E) Mean mPFC signal is illustrated in beta weights averaged across all voxels within the a priori spherical ROI in the SZ-AT group after training. All error bars represent the SEM.
improved reality monitoring and standard outcome measures of verbal memory and of executive function, as these are both known to contribute to source memory performance (e.g., Fisher et al., 2008).

After cognitive training, SZ-AT subjects performed significantly better on delayed verbal memory recall (NAB; Stern and White, 2003) compared to baseline (t(15) = 2.70, p = 0.02; Figure 3A), but no such improvement was found for the SZ-CG group (delayed recall: t(13) = 1.08, p = 0.30). After training, accuracy for overall source memory identification of word items in the SZ-AT subjects was significantly correlated with better delayed verbal memory recall, even after controlling for age, education, and IQ (delayed recall: r = 0.68, p = 0.01) (Figure 3A); however, no such association was present at baseline (delayed recall: r = 0.23, p = 0.45). Furthermore, after cognitive training, mPFC signal within the a priori ROI was significantly correlated with verbal memory scores at 16 weeks (Figure 3B); however, mPFC signal within the a priori ROI in the SZ-AT subjects at baseline did not correlate with delayed recall at baseline (r = −0.04, p = 0.89). No such associations were found in SZ-CG subjects after the intervention (task performance with delayed recall: r = −0.18, p = 0.53; mPFC signal with delayed recall: r = −0.14, p = 0.64). These data indicate that correlations between verbal memory and reality monitoring performance, and between verbal memory and mPFC signal, are the result of the computerized cognitive training.

After cognitive training, the SZ-AT subjects performed significantly better on a measure of executive functioning (Tower of London task; Keefe et al., 2004) compared to baseline (t(15) = 2.47, p = 0.03), a finding not seen in the SZ-CG subjects (t(13) = 0.15, p = 0.89). In SZ-AT subjects, overall source memory identification of word items after training was significantly correlated with performance on executive functioning, even after controlling for age, education and IQ (r = 0.59, p = 0.03), though this association was not present at baseline (r = 0.29, p = 0.28). However, mPFC signal within the a priori ROI at 16 weeks was not associated with executive functioning at 16 weeks (r = 0.31, p = 0.27). No associations between task performance and executive functioning were seen after the intervention in SZ-CG subjects (r = 0.05, p = 0.85). These data indicate that cognitive training induces an improvement in executive function in SZ-AT subjects which is associated with better reality monitoring, but not with greater activation in mPFC.

Clinical symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) which rates each symptom—such as delusions or hallucinations—on a scale of 1 (absent) to 7 (extreme) (Kay et al., 1987). Overall mean symptom ratings were low in this clinically stable group of SZ participants (slightly over 2, mild) at baseline and at 16 weeks (Table 3). There was no significant change in mean symptom ratings at 16 weeks compared to baseline in either the SZ-AT group (t(15) = 0.58, p = 0.57) or in the SZ-CG group (t(13) = 1.62, p = 0.13). Source memory accuracy was not correlated with any reduction in symptom ratings at 16 weeks in the SZ-AT group (r = 0.27, p = 0.30) or in the SZ-CG group (r = 0.31, p = 0.27).

Findings Six Months after the Intervention

In the 13 SZ-AT subjects who returned for reassessment 6 months later (Table 4), there was no overall change in social functioning at a group level (t(12) = 0.49, p = 0.63) as measured by the Quality of Life Scale (QLS) Social Functioning Subscale (Bilker et al., 2003). However, the level of reality monitoring signal within the a priori spherical mPFC ROI immediately after training was significantly correlated with ratings of social functioning at the 6 month follow-up (Figure 4). Reality monitoring signal within the a priori mPFC ROI at baseline did not correlate with ratings of
We do not know which aspects of the cognitive training were most responsible for the behavioral and neural improvements we observed. The reality monitoring task had a strong verbal memory component, and the auditory/verbal learning exercises we employed (for 50 hr of the training) have been shown to improve verbal learning and memory in schizophrenia subjects in a prior study (Fisher et al., 2009) and in the current study (Figure 3A). Indeed, after training, both overall reality monitoring task performance and mPFC signal within the a priori ROI were significantly associated with better verbal memory (Figures 3A and 3B). These findings suggest that training of auditory/verbal learning and memory processes contributes to significant behavioral improvement in reality monitoring as well as improvement in the underlying neural systems that facilitate reality monitoring. However, basic social cognition performance is also strongly correlated with reality monitoring abilities and with activation in mPFC (Benoit et al., 2010; Heberlein et al., 2002; Hooker et al., 2011; Mattavelli et al., 2011; Ochsner et al., 2004, 2005; Phan et al., 2002; Ray et al., 2010; Sabatinelli et al., 2006, 2008).

To our knowledge, this is the first time that a complex higher-order cognitive process in a serious neuropsychiatric illness—in this case, the ability to distinguish the source of information generated by the “self” from information generated by the “other”—has been the targeted outcome of a neuroscience-informed cognitive training strategy. Our study also demonstrates that, for patients with schizophrenia, training of component cognitive processes generalizes to an untrained higher-order operation and produces a significant improvement in its neural correlates, such that patients begin to demonstrate more “normal” brain-behavior associations, which in turn predict better social functioning several months later. Thus, it is possible to significantly improve brain function in schizophrenia, even in patients who have been ill for an average of 20 years, and it appears that these improvements set the stage for an enduring improvement in social functioning that occurs even in the absence of other psychosocial therapies. Of note, schizophrenia participants showed a range of responses to the intervention, and even after 80 hr of intensive training, and despite significant increases in mPFC activation, they still did not demonstrate the same activation levels as those observed in healthy comparison subjects. Though not all patients respond equally well to cognitive training, a successful response appears to open a critical window for further functional gains, consistent with our previous finding that patients with higher general cognitive improvement after training show significantly better overall quality of life ratings at 6 months (Fisher et al., 2010).

DISCUSSION

Schizophrenia patients who received intensive computerized training of component auditory/verbal, visual, and social cognitive processes, compared to patients who played computer games, showed: (1) a significant improvement in their accuracy performing a complex reality monitoring task that was not part of the training exercises (i.e., generalization of training effects); (2) a significant increase in mPFC activation during performance of this task; (3) a significant association between the level of mPFC activation and task performance (findings that were not present at baseline); and (4) a significant relationship between mPFC activation after training and better social functioning 6 months later. Our findings are consistent with prior work indicating that medial prefrontal dysfunction is associated with poor self-reflection processes, poor social cognition, and poor social functional status in schizophrenia (Holt et al., 2011; Lee et al., 2006; Park et al., 2008), but indicate that—rather than being a static deficit—this neural system impairment is responsive to an intensive cognitive training intervention.

To our knowledge, this is the first time that a complex higher-order cognitive process in a serious neuropsychiatric illness—in this case, the ability to distinguish the source of information generated by the “self” from information generated by the “other”—has been the targeted outcome of a neuroscience-informed cognitive training strategy. Our study also demonstrates that, for patients with schizophrenia, training of component cognitive processes generalizes to an untrained higher-order operation and produces a significant improvement in its neural correlates, such that patients begin to demonstrate more “normal” brain-behavior associations, which in turn predict better social functioning several months later. Thus, it is possible to significantly improve brain function in schizophrenia, even in patients who have been ill for an average of 20 years, and it appears that these improvements set the stage for an enduring improvement in social functioning that occurs even in the absence of other psychosocial therapies. Of note, schizophrenia participants showed a range of responses to the intervention, and even after 80 hr of intensive training, and despite significant increases in mPFC activation, they still did not demonstrate the same activation levels as those observed in healthy comparison subjects. Though not all patients respond equally well to cognitive training, a successful response appears to open a critical window for further functional gains, consistent with our previous finding that patients with higher general cognitive improvement after training show significantly better overall quality of life ratings at 6 months (Fisher et al., 2010).

We do not know which aspects of the cognitive training were most responsible for the behavioral and neural improvements we observed. The reality monitoring task had a strong verbal memory component, and the auditory/verbal learning exercises we employed (for 50 hr of the training) have been shown to improve verbal learning and memory in schizophrenia subjects in a prior study (Fisher et al., 2009) and in the current study (Figure 3A). Indeed, after training, both overall reality monitoring task performance and mPFC signal within the a priori ROI were significantly associated with better verbal memory (Figures 3A and 3B). These findings suggest that training of auditory/verbal learning and memory processes contributes to significant behavioral improvement in reality monitoring as well as improvement in the underlying neural systems that facilitate reality monitoring. However, basic social cognition performance is also strongly correlated with reality monitoring abilities and with activation in mPFC (Benoit et al., 2010; Heberlein et al., 2008; Hooker et al., 2011; Mattavelli et al., 2011; Ochsner et al., 2004, 2005; Phan et al., 2002; Ray et al., 2010; Sabatinelli et al., 2006, 2008).

Table 3. Neuropsychological Measures and Clinical Symptom Ratings at Baseline and after 16 Weeks of Intervention in SZ-AT Subjects and SZ-CG Subjects

<table>
<thead>
<tr>
<th></th>
<th>SZ-AT (n = 16)</th>
<th>SZ-CG (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>16 Weeks</td>
</tr>
<tr>
<td>Delayed verbal memory recall (z score)</td>
<td>-1.06 (1.54)</td>
<td>-0.21&lt;sup&gt;a&lt;/sup&gt; (1.27)</td>
</tr>
<tr>
<td>Tower of London (z score)</td>
<td>-0.13 (1.12)</td>
<td>0.39&lt;sup&gt;b&lt;/sup&gt; (0.86)</td>
</tr>
<tr>
<td>Clinical symptom ratings (1 = absent, 7 = extreme)</td>
<td>2.57 (0.67)</td>
<td>2.59 (0.68)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD).

<sup>a</sup>Paired two-tailed t tests indicate that SZ-AT subjects showed significant improvement on delayed verbal memory recall at 16 weeks compared to baseline (p = 0.02). SZ-CG subjects showed no significant improvement in this measure (p = 0.30).

<sup>b</sup>SZ-AT subjects also showed significant improvement on the Tower of London task at 16 weeks compared to baseline (p = 0.03); SZ-CG subjects showed no significant improvement in this measure (p = 0.89).

Table 4. Ratings on QLS Social Functioning Subscale for SZ-AT Subjects and SZ-CG Subjects at Baseline and 6 Months after the Intervention Was Completed

<table>
<thead>
<tr>
<th></th>
<th>SZ-AT (n = 13)</th>
<th>SZ-CG (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.76 (1.70)</td>
<td>2.54 (1.74)</td>
</tr>
<tr>
<td>Social functioning 6 months after intervention (0 = virtually absent, 6 = adequate functioning)</td>
<td>2.20 (1.77)</td>
<td>2.08 (1.84)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD).
neuronal training can begin to "normalize" abnormal brain-behavior as 
reported by Fischer et al. (2009). Also, participants rated their experiences 
as highly enjoyable and beneficial. When compared to the control condition, 
participants demonstrated improved executive functioning after training, 
which persisted even in non-clinically stable patients. These results suggest 
that intensive training of component cognitive processes in schizophrenia 
can increase the efficiency of a complex reality monitoring source memory 
operation in clinically stable patients. Taken together, these findings indicate 
that better executive functioning after training and improved social 
functioning 6 months later.

**EXPERIMENTAL PROCEDURES**

**Subjects**

The subjects in this study included 31 clinically stable, voluntarily 
interested, and non-institutionalized schizophrenia patients (SZ: mean age 
= 40 years; education = 13 years; IQ = 103; illness duration = 19.4 years) 
drawn from our randomized clinical trial of cognitive-training (ClinicalTrials.gov 
NCT00312962) and 16 healthy comparison subjects matched to the SZ subjects 
at a group level in age, gender, and education (HC: mean age = 45 years; IQ = 115) (Table 1). SZ 
subjects were recruited from community mental health centers and outpatient 
clinics, and HC subjects were recruited via advertisement. Inclusion criteria 
were Axis I diagnosis of schizophrenia (determined by the Structured Clinical 
Interview for DSM-IV (SCID)) (First et al., 2002) or, for HC subjects, no Axis I or 
Axis II psychiatric disorder (SCID—Nonpatient edition), no substance dependence 
or current substance abuse, good general physical health, age between 18 and 
60 years, and English as first language. All subjects gave written informed 
consent for a protocol approved by the Committees on Human Research 
at the University of California, San Francisco, and at the Department of 
Veterans Affairs Medical Center and then underwent a series of baseline 
behavioral assessments and imaging. One HC provided only behavioral data 
because he was too claustrophobic to be scanned. All others participated in 
a baseline fMRI session. SZ subjects were then stratified by age, education, 
and symptom severity and randomly assigned to either 80 hr of active 
training (SZ-AT) or 80 hr of a computer games control condition (SZ-CG). SZ 
subjects were blind to group assignment. There were no significant differences 
between the two patient groups at baseline in antipsychotic medications (first 
generation, second generation, multiple, or none), in Cogentin or chlopramidine 
equivalents, or in the number of subjects in each group taking antidepressants, 
mood stabilizers, benzodiazepines, or anticholinergic medications (Table 2). All SZ 
subjects had outpatient status for at least 6 months prior to study entry 
and no significant medication changes (dosage change <10%) during 
the study. One SZ-CG subject withdrew from the study for personal reasons 
following baseline and 16 weeks; one SZ-AT subject felt too anxious to 
complete the reality monitoring experiment in the scanner at 16 weeks, 
and thus performed the task outside the scanner, providing only behavioral data.

Thirteen out of 15 SZ-AT subjects and 12 out of 14 SZ-CG subjects returned 
to the laboratory 6 months later to receive follow-up clinical assessments.

The 2 SZ-AT subjects and the 2 SZ-CG subjects who did not return were 
unavailable and/or unwilling to be involved in further study participation.

None of the 13 SZ-AT or the 12 SZ-CG subjects had participated in any new 
psychosocial treatment program during the no-contact period.

**Assessments**

All SZ subjects received clinical and cognitive assessments at baseline and 
after training. Clinical symptoms were assessed with the Positive and Negative 
Syndrome Scale (Kay et al., 1987), which rates each symptom on a scale of 1 = absent 
to 7 = extreme. Verbal memory and executive functioning was assessed 
with the NAB Daily Living Memory Scale (Starr and White, 2003) and the 
BACS Tower of London test (Keefe et al., 2004; Table 3). Raw scores were 
converted to age-adjusted z scores using normative data, published by 
the test authors. Social functioning was assessed with the QLS 6 months 
after the cognitive training was completed (Bikker et al., 2003; Table 4). 
The QLS is a semistructured interview that assesses functioning during 
the preceding 4 weeks on a scale of 0 = virtually absent to 6 = adequate 
functioning. Researchers who randomized subjects were independent from 
assessment personnel, and all assessment staff were blind to subjects' group 
assignment. The PANSS and QLS were conducted by two assessment staff...
Computerized Cognitive Training

Complete details on the computerized cognitive training exercises are presented in the Supplemental Experimental Procedures available online. In brief, cognitive training consisted of a module of auditory processing exercises (http://www.postscience.com/our-products/brain-fitness-program), a module of visual processing exercises (http://www.postscience.com/our-products/demo), and a module of computerized emotion identification exercises, composed of training in facial emotion recognition and theory of mind (MindReading, MicroExpressions Training Tool, Subtle Expressions Training Tool; Baron-Cohen et al., 2003; Eckman, 2003). The SZ-AT subjects participated in auditory exercises for 1 hr a day for a total of 50 hr (10 weeks), and then participated in visual exercises for 1 hr a day for a total of 30 hr (6 weeks) that were combined with 15 min per day of emotion identification exercises (total of 10 hr). In the exercises, patients were driven to make progressively more accurate discriminations about the spectro-temporal fine-structure of auditory and visual stimuli under conditions of increasing working memory load, or of basic social cognitive stimuli under progressively brief presentations, and to incorporate and generalize those improvements into working memory rehearsal and decision-making. The auditory and visual exercises were continuously adaptive: they first established the precise parameters within each stimulus set required for an individual subject to maintain 80% correct performance, and once that threshold was determined, task difficulty increased systematically and parametrically as performance improved. The social cognition training was partially adaptive, in that difficulty level increased progressively as participants successfully completed blocks of trials at a given difficulty level. The design and implementation of this approach was informed by research demonstrating impairments in schizophrenia in basic auditory and visual perceptual processes, as well as in higher-order working memory and social cognitive functions (e.g., Green, 1996; Javitt, 2009; Javitt et al., 2000). In the computer games control condition, SZ-CG subjects systematically rotated through 16 different commercially available computer games (i.e., clue-gathering and visual-spatial puzzle games such as Hangman, Tic-Tac-Toe, Tetris) for a total of 80 hr over 16 weeks. The control condition was designed to allow for nonspecific motivation, engagement, and deployment of attentional and executive functioning resources, without providing constrained, intensive, and adaptive training on specific cognitive operations. Subjects rated both conditions as equally entertaining on self-report questionnaires, and subjectively found both conditions to be equally beneficial; a prior study found excellent maintenance of the study blind with this protocol (Fisher et al., 2009).

fMRI Stimulus Presentation

Visual fMRI stimuli were presented with E-Prime (http://www.pstnet.com/prime.cfm) and back-projected using an LCD projector onto a screen at the foot of the scanner table. Subjects viewed the screen using a mirror attached to the head coil and made finger-press responses on a fiber-optic eight-channel response pad (Lightwave Medical Industries Ltd., Vancouver, BC, Canada). The response pad device collected scanner TTL pulses generated at the onset of MR acquisition. Subject responses and scanner signals were recorded by the E-Prime presentation program, allowing for precise retrospective temporal synchronization of stimulus events and image acquisition.

Image Acquisition

fMRI activity was measured on a 3 Tesla General Electric Signa LX 15 scanner and eight channel head coil. Functional imaging consisted of blood oxygen level-dependent (BOLD) sensitive images acquired during performance of the experimental task, using a spiral sequence (TR = 1 s; TE = 30 ms; flip angle = 60, matrix = 64 x 64, FOV = 22 cm, 14 slices, 6 mm thickness). Stimulus duration was 1 s, with a 7-s variable interstimulus interval during which subjects fixated on a cross. Image analysis was performed using MATLAB (Mathworks Inc.) and SPM2 software (http://www.fil.ion.ucl.ac.uk/spm).

Statistical Analyses: fMRI Data

Images were realigned to correct for motion artifacts using a six-parameter rigid body affine transformation. The resulting images were normalized to a standard stereotactic space (Montreal Neurological Institute [MINI] Template) using a 12 parameter affine/non-linear transformation and spatially smoothed with a 10mm full-width half maximum isotropic Gaussian kernel. Data were submitted to a general linear model analysis, fitting a reference canonical hemodynamic response function (hrf) to each event. Correct and incorrect trials were modeled separately. Image intensity was scaled to the mean global intensity of each time series. To examine mPFC fMRI activity during reality monitoring, we defined an a priori 20 mm (radius) spherical ROI according to Cabeza et al. (2004) locus of mPFC activity, for self-referral memory reported in a sample of psychiatrically healthy subjects, centered on −4, 52, 8 Talairach coordinates. We first conducted multiple one-sample t tests within each group (HC, SZ-CG, and SZ-AT) at baseline to compare reality monitoring activity (i.e., activity for correctly identified self-generated items versus activity for correctly identified externally presented items) on a voxel-by-voxel basis, using the spherical a priori mPFC ROI as an explicit mask. Multiple comparison corrections were then performed within the mPFC ROI, with the FWE correction of p < 0.05 and with a cluster extent of 0, using the SVC implemented in SPM2. This comparison between self-generated and externally presented items was used because the deficit in correctly identifying the source of self-generated information is one of the most striking clinical findings in schizophrenia; furthermore, prior studies indicate that schizophrenia patients are significantly impaired at identifying the source of self-generated items but not externally presented items, compared to healthy subjects (Bentall et al., 1991; Vinogradov et al., 2008). Next, mean beta weights (i.e., signal levels) from the self-generated versus externally presented contrast, were extracted across all voxels within the a priori spherical mPFC ROI for each group at baseline. These mean beta weights were submitted to a one-way ANOVA in SPSS to test for mPFC signal differences between the HC, SZ-CG, and SZ-AT subject groups at baseline. These mPFC mean beta weights from the self-generated versus externally presented comparison that were extracted across the a priori spherical mPFC ROI for each group at baseline were then correlated with behavioral performance for each group (HC, SZ-CG, and SZ-AT) at baseline.

Next, on a voxel-by-voxel basis, we performed one-way within-subject ANOVAs to compare reality monitoring activity before and after intervention for each group, using the spherical a priori mPFC ROI as an explicit mask. Multiple comparison corrections were then performed within the mPFC ROI, with the FWE correction of p < 0.05 and with a cluster extent of 0, using the SVC implemented in SPM2. These voxel-based analyses were used to reveal within-group intervention-based effects at 16 weeks versus baseline for each group. Next, in order to investigate whether any between-group differences in mPFC signal were specifically associated with the cognitive training, mean beta weights for the self-generated versus externally presented contrast were extracted across all voxels within a priori spherical mPFC ROI for each group (HC, SZ-CG, and SZ-AT) and for each session (i.e., at baseline and at 16 weeks). These mPFC mean beta weights within the a priori spherical mPFC ROI were submitted to a repeated-measures group-by-session ANOVA in SPSS to test for differences between the HC, SZ-CG, and SZ-AT groups in mPFC signal change from baseline to 16 weeks. Next, these mPFC mean beta weights from the self-generated versus externally presented comparison that were extracted across the a priori spherical mPFC ROI for...
each group at 16 weeks were correlated with behavioral performance for each group at 16 weeks. See Figure S1 and Table S1 for whole brain analyses of the self-generated condition versus the externally presented condition at baseline in (A) HC and (B) SZ subjects, and see Figure S2 and Table S2 for whole-brain signal change at 16 weeks versus baseline in (A) SZ-AT, (B) SZ-CG, and (C) HC subjects.

SUPPLEMENTAL INFORMATION

Supplemental Information includes two figures, two tables, and Supplemental Experimental Procedures and can be found with this article online at doi:10.1016/j.neuron.2011.12.024.

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