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Intensive cognitive training in schizophrenia enhances working memory and associated prefrontal cortical efficiency in a manner that drives long-term functional gains

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ABSTRACT

We investigated whether intensive computerized cognitive training in schizophrenia could improve working memory performance and increase signal efficiency of associated middle frontal gyri (MFG) circuits in a functionally meaningful manner. Thirty schizophrenia participants and 13 healthy comparison participants underwent fMRI scanning during a letter *N*-back working memory task. Schizophrenia participants were then randomly assigned to either 80 h (16 weeks) of cognitive training or a computer games control condition. After this intervention, participants completed a second fMRI *N*-back scanning session. At baseline, during 2-back working memory trials, healthy participants showed the largest and most significant activation in bilateral MFG, which correlated with task performance. Schizophrenia participants showed impaired working memory, hypoactivation in left MFG, and no correlation between bilateral MFG signal and task performance. After training, schizophrenia participants improved their 2-back working memory performance and showed increased activation in left MFG. They also demonstrated a significant association between enhanced task performance and right MFG signal, similar to healthy participants. Both task performance and brain activity in right MFG after training predicted better generalized working memory at 6-month follow-up. Furthermore, task performance and brain activity within bilateral MFG predicted better occupational functioning at 6-month follow-up. No such findings were observed in the computer games control participants. Working memory impairments in schizophrenia and its underlying neural correlates in MFG can be improved by intensive computerized cognitive training; these improvements generalize beyond the trained task and are associated with enduring effects on cognition and functioning 6 months after the intervention.

Introduction

Individuals with schizophrenia experience prominent working memory deficits that have deleterious functional consequences (Green et al., 2000; Takahashi et al., 2005; Tan, 2009). Compared to healthy participants, they show both hypoactivation (Barch et al., 2001; Carter et al., 1998; Perlstein et al., 2003; Stone et al., 1998; Weinberger and Berman, 1996) and hyperactivation (Callicott et al., 2000) of dorsolateral prefrontal cortex (i.e., bilateral middle frontal gyri) when performing different working memory tasks, indicating abnormal and inefficient recruitment of prefrontal neural resources as working memory demands increase (Callicott et al., 2000; Minzenberg et al., 2009). In a meta-analytic review across 124 studies, working memory deficits were consistently found in schizophrenia patients regardless of stimulus modality, indicating that they may represent a cardinal cognitive endophenotype of the illness (Lee and Park, 2005). Enhancement of working memory is now seen as a critical treatment target, but has thus far not been amenable to psychopharmacologic interventions (Buchanan et al., 2005; Goldberg et al., 2007; Mishara and Goldberg, 2004; Vinogradov et al., 2013).

Four prior studies have examined both the behavioral and prefrontal cortical activation effects of several forms of cognitive remediation for working memory dysfunction in participants with schizophrenia (Bor et al., 2011; Haut et al., 2010; Wexler et al., 2000; Wykes et al., 2002): Wexler et al. (2000) studied eight patients before and after 10 weeks of computerized verbal working memory exercises; Wykes et al. (2002) studied six patients receiving 40 h of therapist coaching in executive functioning versus six patients in occupational therapy; Bor et al. (2011) studied eight patients receiving 28 h of computerized cognitive remediation therapy on a verbal and a spatial *N*-back task

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versus nine patients receiving no additional treatment; and Haut et al. (2010) studied nine patients receiving 25 h of computerized training on a word N-back task versus nine patients receiving group-based social skills training. All four studies showed increased prefrontal activation as a result of cognitive remediation; additionally, Haut et al. (2010) showed that the nine patients who received word N-back training also improved performance on an animal picture N-back task which correlated with increased activation in bilateral prefrontal regions. However, increased prefrontal activation may not necessarily always be indicative of increased prefrontal efficiency (Koch et al., 2006), particularly in light of mixed findings of both prefrontal hypoactivation and hyperactivation in schizophrenia patients compared with healthy participants (Callicott et al., 2000; Perlstein et al., 2003). Thus, despite the promising findings from earlier cognitive remediation studies, the brain mechanisms underlying critical behavioral changes remain unclear.

In an earlier study, we showed that intensive cognitive training of auditory/verbal, visual and social cognitive processes generalized to improvement in an untrained reality monitoring task and increased medial prefrontal cortical (mPFC) activation during performance of this task (Subramaniam et al., 2012). While these findings showed that the neural system impairments of schizophrenia are not immutable, several questions were unanswered. The use of a reality monitoring task did not allow us to probe lateral prefrontal cortical functioning and enhancement of verbal working memory—which was the target of a significant portion of the cognitive training exercises. Thus, while our findings suggested that medial prefrontal cortical regions came "on-line" after training in support of enhanced reality monitoring performance, we were not able to investigate whether or not training enhanced capacity and/or efficiency in key neural systems that were directly targeted by the exercises, nor whether any such enhancement generalized to improved clinical and functional status.

In the present study, we sought to address these questions. We performed fMRI during an untrained N-back working memory task before and after schizophrenia patients were randomized either to intensive computerized cognitive training of auditory/verbal, visual and social cognitive processes or to a rigorously matched computer games control condition. We hypothesized that, compared to the control condition, subjects who underwent cognitive training would show:

1) Improvements on the untrained letter N-back task, suggesting generalization of the effects of training.
2) Restoration of more normal brain–behavior relationships between middle frontal gyrus activation and N-back working memory accuracy, indicating improved lateral prefrontal system efficiency.
3) An association between working memory gains and lower disorganized symptoms, suggesting an impact of cognitive training on clinical status.
4) An association between working memory gains and behavioral improvements at 6-month follow-up, indicating enduring benefits of intensive cognitive training.

Methods and materials

Participants and procedure

Thirty clinically stable volunteer schizophrenia patients (SZ: mean age = 41 years; education = 13 years; IQ = 103; illness duration = 19.4 years) who were willing to undergo fMRI, were recruited from our randomized clinical trial of cognitive training in schizophrenia (ClinicalTrials.gov NCT00312962). This subset of participants who were willing to undertake serial fMRI received the same intervention and all the same behavioral neuropsychological assessments as participants in the parent trial (Fig. 1). These participants who completed fMRI were also matched on demographic variables (i.e., age, education, IQ) to participants in the parent trial. The participants and training procedure are identical to those described in Subramaniam et al. (2012). We report here the results of a working memory fMRI experiment investigating dorsolateral prefrontal cortical systems, in contrast to our prior report on the results of a reality-monitoring experiment investigating medial prefrontal cortical systems (Subramaniam et al., 2012).

SZ participants who underwent fMRI were matched to 15 healthy comparison participants (HC) at a group level on age, gender, and education (Table 1). SZ participants were stratified by age, education, gender, and symptom severity and then randomly assigned to either active computerized cognitive training (SZ-AT), or a control condition of commercial computer games (SZ-CG), performed for 80 h. SZ subjects were blind to group assignment. There were no significant differences in medications between the two patient groups at baseline and no significant medication changes (dosage change < 10%) during the study (Table 2). SZ participants also underwent clinical and neuropsychological assessments by personnel blind to group assignment, at baseline, after the intervention, and at 6-month follow-up (Table 3).

At baseline, two HC participants felt too claustrophobic to remain in the scanner, and provided only behavioral data. All other participants were scanned using fMRI while performing the N-back task. Sixteen weeks later, 15 SZ-AT, 13 SZ-CG, and 12 HC participants completed a second fMRI N-back session. One SZ-AT and 1 SZ-CG were unavailable/unwilling to perform the fMRI N-back task at the second time point, and fMRI data from 1 HC was later excluded due to poor signal. Six months later, 13 SZ-AT and 12 SZ-CG participants returned for cognitive and clinical re-assessment.

Assessments

Symptom severity in schizophrenia was assessed with the Positive and Negative Syndrome Scale (PANSS), which rates each symptom on a scale of 1 (absent) to 7 (extreme) (Kay et al., 1987). Verbal working memory was assessed at 6-month follow-up with the letter–number span from the MATRICS neurocognitive battery (Nuechterlein et al., 2008), a verbal working memory test in which respondents hear strings of letters and numbers and repeat these to the administrator in a particular order. Real-life functioning was assessed with the Quality of Life Scale (QLS) (Bilker et al., 2003). The QLS is a semi-structured interview that assesses functioning during the preceding 4 weeks on a scale of 0 = virtually absent to 6 = adequate functioning, and is used to reference the general well-being of individuals in their day-to-day environment. Research staff who conducted neurocognitive testing or PANSS and QLS interviews first completed extensive training on testing/interviewing and scoring criteria of individual items (e.g., scoring videotaped sessions, observation of sessions conducted by experienced staff, and participating in mock sessions). Intraclass correlation coefficients (ICCs) were greater than 0.85 for the PANSS and QLS total and subscale scores. The MATRICS battery demonstrates an ICC of 0.79 for working memory (Keefe et al., 2011).

Computerized cognitive training

The SZ-AT participants completed two sequential modules of adaptive computerized cognitive training exercises, 1 h a day for 80 h over 16 weeks. SZ-AT subjects first participated in a module of auditory/verbal processing exercises (http://www.positscience.com/our-products/brain-fitness-program), for 1 h a day for a total of 50 h (10 weeks). Next, SZ-AT participants completed a module of visual processing exercises (http://www.positscience.com/our-products/demo), together with 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) for 1 h a day for a total of 30 h (6 weeks). 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

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