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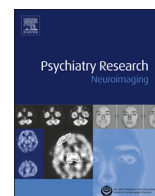
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The influence of combined cognitive plus social-cognitive training on amygdala response during face emotion recognition in schizophrenia

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ABSTRACT

Both cognitive and social-cognitive deficits impact functional outcome in schizophrenia. Cognitive remediation studies indicate that targeted cognitive and/or social-cognitive training improves behavioral performance on trained skills. However, the neural effects of training in schizophrenia and their relation to behavioral gains are largely unknown. This study tested whether a 50-h intervention which included both cognitive and social-cognitive training would influence neural mechanisms that support social cognition. Schizophrenia participants completed a computer-based intervention of either auditory-based cognitive training (AT) plus social-cognition training (SCT) ($N=11$) or non-specific computer games (CG) ($N=11$). Assessments included a functional magnetic resonance imaging (fMRI) task of facial emotion recognition, and behavioral measures of cognition, social cognition, and functional outcome. The fMRI results showed the predicted group-by-time interaction. Results were strongest for emotion recognition of happy, surprise and fear: relative to CG participants, AT+SCT participants showed a neural activity increase in bilateral amygdala, right putamen and right medial prefrontal cortex. Across all participants, pre-to-post intervention neural activity increase in these regions predicted behavioral improvement on an independent emotion perception measure (MSCEIT: Perceiving Emotions). Among AT+SCT participants alone, neural activity increase in right amygdala predicted behavioral improvement in emotion perception. The findings indicate that combined cognition and social-cognition training improves neural systems that support social-cognition skills.

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1. Introduction

Cognitive deficits are among the most treatment resistant and functionally debilitating aspects of schizophrenia (Green, 2007). Although many cognitive skills are related to functional outcome, social-cognitive skills, such as facial emotion recognition, are recognized as one of the strongest predictors of functioning (Hooker and Park, 2002). Cognitive and social-cognitive behavioral impairments arise from abnormalities in underlying neural mechanisms supporting these processes (Aleman and Kahn, 2005; Barch, 2005). Social cognition is supported by a neural system which includes the amygdala, superior temporal cortex (STC), somatosensory-related cortex (SRC), and medial prefrontal cortex (MPFC) (Adolphs, 2009, 2010). Because psychopharmacological

treatments alone have not succeeded in dramatically improving cognition (Keefe et al., 2007) or social cognition (Swartz et al., 2007), there is considerable interest in identifying whether targeted training in cognition and social-cognition can improve behavioral performance, restore dysfunctional neural mechanisms, and ultimately provide long-lasting functional benefits.

Animal models of learning-induced neuroplasticity suggest that benefits of behavioral training occur from a dynamic interplay between neural processing and behavioral experience (Buonomano and Merzenich, 1998; Ohl and Scheich, 2005). Behavioral training in a specific cognitive-perceptual domain (e.g. discriminating auditory tones) induces neural changes, such as neuronal tuning and cortical expansion, and these changes result in better detection and processing of sensory stimuli (Polley et al., 2006; Zhou and Merzenich, 2007). Human neuroimaging studies show evidence of this process in multiple domains. Neural structure increases and/or function improves in temporo-parietal motion perception regions after concentrated juggling (Draganski et al., 2004), auditory cortices after musical training (Wan and Schlaug, 2010), and lateral prefrontal

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cortex after memory training (Klingberg, 2010). Across these different domains, neural change predicts improvement in behavioral performance, suggesting that training-induced changes to underlying neural systems support more efficient neural processing and better behavioral skills.

While substantial evidence demonstrates that cognitive and social-cognitive remediation interventions improve behavioral performance in schizophrenia (Wykes et al., 2011; Kurtz and Richardson, 2012), there is little research on the neural effects of these interventions. Until recently, neural deficits associated with schizophrenia were considered a permanent consequence of the disease. However, initial studies of early and late-stage schizophrenia indicate that compromised neurocognitive systems show neuroplastic changes after cognitive and social-cognitive training and neural changes are related to behavioral improvement (Eack et al., 2010; Subramaniam et al., 2012). Although these new findings have exciting treatment implications, crucial questions remain regarding which neurocognitive systems to target, what neural changes occur, and how neural changes support functional benefits.

The goal of the current study was to identify whether a computer-based training intervention which targeted both cognitive and social-cognitive skills in people with schizophrenia would influence neural regions that support facial emotion recognition, particularly the amygdala. This goal and the methods used to address it build on our prior research. The auditory-based cognitive training (AT) program targets verbal learning and memory and has been previously studied by our group (Fisher et al., 2009; Vinogradov et al., 2012). AT improves verbal learning/verbal memory deficits through progressive training in auditory processing and verbal working memory. In a randomized clinical trial, schizophrenia participants who completed 50 h of AT (versus non-specific computer games) showed behavioral improvements in verbal learning/verbal memory and global cognition, as well as changes in magnetoencephalographic indices of early neural processing (Vinogradov et al., 2012). However, AT participants did not show improvements in social cognition (Fisher et al., 2009). Thus, follow-up studies included social cognition training (SCT), targeting facial emotion recognition and basic theory of mind. Schizophrenia participants who completed a training regimen that combined AT+SCT versus computer-games, had behavioral improvement in both cognition and social-cognition (Hooker et al., 2012; Subramaniam et al., 2012; Sacks et al., 2013). Neural improvement was also evident; after AT+SCT, SRC activity increased during facial emotion recognition (Hooker et al., 2012), and in a separate study using a broader range of training, MPFC activity increased during reality monitoring (Subramaniam et al., 2012). In both studies, neural changes predicted behavioral improvements.

Facial emotion recognition is a foundational social-cognitive process with a well-defined neurocognitive system that includes the amygdala, STC, and SRC (Adolphs et al., 2003). These regions are more active during face emotion recognition than face identity recognition or other face judgments (Vuilleumier and Pourtois, 2007), and a lesion (in any region) disrupts emotion recognition but not other aspects of face processing (Adolphs, 2010; Adolphs et al., 2000; Pitcher et al., 2008). The broader network includes structures involved in social-emotional processing more generally, such as the fusiform gyrus, MPFC, and striatum (Calder and Young, 2005; Heberlein et al., 2008). In addition to severe behavioral deficits, people with schizophrenia have neural abnormalities in nearly all facial emotion processing regions (Gur et al., 2007a; Habel et al., 2010a; Hooker et al., 2011; Seiferth et al., 2009; Williams, 2008), with amygdala, striatum, and fusiform gyrus as the regions most consistently less active for schizophrenia participants relative to healthy controls (Li et al., 2010).

Most research has focused on the amygdala. Schizophrenia participants have abnormally low amygdala activity during face

emotion processing (Li et al., 2010), and both lower activity (Gur et al., 2007b) and lower gray matter volume (Namiki et al., 2007) are related to worse emotion recognition. Abnormally high amygdala activity has also been observed and is associated with the misinterpretation of neutral and emotional stimuli (Gur et al., 2007b; Holt et al., 2005). Overall, the data suggest that amygdala activity in schizophrenia is not appropriately harnessed in service of accurate emotion recognition.

Our prior study of emotion recognition before and after AT+SCT used an fMRI task with a blocked presentation of positive and negative emotions and found that activity in the postcentral gyrus, a region of the SRC, increased more after AT+SCT than computer-games, but there were no significant amygdala changes. Inability to separate correct and incorrect trials in the blocked design and other methodological factors might have masked intervention-related effects in the amygdala. The present study used an fMRI task and neuroimaging methods more likely to engage and reveal amygdala activity.

Schizophrenia participants completed a 50-h computer-based intervention of auditory training plus social-cognition training (AT+SCT) or non-specific computer-games (CG). The CG placebo consisted of engaging computer-games that did not target cognitive improvement and was designed to control for auxiliary aspects of AT+SCT, including sustained attention on a computer task, staff contact, and monetary payments. Controlling these non-essential features, theoretically, isolates components of AT+SCT that are crucial for learning-induced neuroplasticity (i.e. targeted, progressive training in a specific neurocognitive skill).

Assessments before and after the intervention included standardized cognitive and social-cognitive tests, an interview-based assessment of daily functioning, and an event-related fMRI task of emotion recognition. The goal was to test intervention effects during correct identification of the six basic emotional expressions (happy, surprise, fear, angry, disgust, and sad). Neuroimaging acquisition and analysis parameters optimized amygdala signal. Hypotheses were as follows: (1) Neural activity in emotion processing regions would increase more after AT+SCT than after CG; and (2) Intervention-related neural activity increase in these regions would predict better emotion recognition and better daily functioning.

2. Methods

This study ran in parallel with our larger randomized controlled trial of cognitive training in schizophrenia at the University of California San Francisco (UCSF)/SFVA (ClinicalTrials.gov NCT00312962). Recruitment and initial contact occurred through the parent study and interested participants were invited to do an additional imaging study at UC Berkeley.

2.1. Participants and behavioral assessments

Schizophrenia participants were recruited from community centers and outpatient clinics. Participants had outpatient status for 3 months and no significant medication changes during the study. After the research was explained, participants gave written informed consent and underwent baseline assessments over 4–5 weeks. The UC Berkeley and San Francisco ethical review boards approved the study. Twenty-eight participants expressed interest in fMRI; two participants did not complete training, two did not return for the post-training scan, and two had unusable data for at least one time point. The final fMRI sample included $N=22$ ($N=11$ AT+SCT/ $N=11$ CG). Demographics from this sample are also reported in Hooker et al. (2012).

Diagnosis was assessed via information from the Structured Clinical Interview for DSM-IV Disorders (SCID) (First et al., 2002), caretakers, medical team, and medical record. IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). Pre/post behavioral assessments included: Positive and Negative Syndrome Scale-Extended (PANSS-E) (Kay et al., 1987); Quality of Life Scale-Abbreviated (QLS) (Bilker et al., 2003); MATRICS Global Cognition score for cognitive performance (Nuechterlein et al., 2008); and Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) Perceiving Emotions subscale for emotion

processing (Mayer et al., 2003). The MSCEIT Perceiving Emotions subscale involves identifying emotions in faces, paintings, and landscapes without constraints on presentation or response time. Diagnosis, PANSS-E, and QLS ratings were reached by consensus between two raters (ICC > 0.85). Behavioral assessments and group assignment were conducted at UCSF/SFVA in the context of larger behavioral studies, where participants were stratified by baseline age, education, gender, and symptom severity, and approximately matched pairs of participants were randomly assigned to the active or placebo intervention. From this larger pool of subjects, participants who were MR compatible and interested in additional research opportunities were referred to the imaging study at UC Berkeley. Inclusion criteria were as follows: schizophrenia or schizoaffective disorder, age 18–60 years, and English as primary language. Exclusion criteria were as follows: IQ < 70, prior head trauma, neurological or medical illness, or substance dependence (past 6 months).

In the final sample ($N=22$), AT+SCT participants were older than CG participants [Age: AT+SCT=51.2(5.8); CG=41.0(8.4), $t(21)=3.3$, $p=0.004$]. Groups did not differ on any other demographic or clinical characteristic (all $t_s < 1$, $p_s > 0.3$, unless noted). [Variable=Mean(SD): Gender: AT+SCT=1F/10M; CG=3F/8M; Education: AT+SCT=13.7(2.2); CG=12.8(2.5); WASI: AT+SCT=98.2(18.7); CG=103.6(19.4); Diagnosis: AT+SCT=5 SZ-Aff; 6 SZ; CG=4 SZ-Aff; 7 SZ; Illness duration: AT+SCT=28.0(8.3); CG=20.6(11.6) $t(21)=1.3$, $p=0.16$; Chlorpromazine equivalent: AT+SCT=252.5(339); CG=371.4(456); PANSS Total: AT+SCT=76.2(15.4); CG=68.1(16.3)]. Chlorpromazine equivalents were identified according to standard calculations (Hales and Yudofsky, 2002). Medication type (including those for mood anxiety, etc.) did not differ between groups.

2.2. Intervention

2.2.1. Auditory training (AT)

The AT program was developed by Posit Science Corporation (<http://www.positscience.com>) and consists of computerized exercises structured to improve auditory and verbal information processing. In initial exercises, participants make progressively difficult distinctions between speech-related sounds. Subsequent exercises require participants to distinguish and encode increasingly complex auditory/verbal stimuli and to manipulate these stimuli in working memory. Difficulty level is continuously adjusted to maintain ~80% accuracy. See Fisher et al (2009) for additional information. Posit Science Corporation provided the software but had no other role in the research.

2.2.2. Social-cognition training (SCT)

The SCT program consists of exercises from two commercially available software packages: Micro-Expression and Subtle Expressions Training Tool (METT–SETT) (<http://face.paulekman.com>), and MindReading (Baron-Cohen et al., 2003; Ekman, 2003). Training engaged both perceptual and executive control processes related to emotion recognition. Each training session covered one to four specific emotion(s), and focused on facial expressions. Exercises began with easy, instructive trials, and became increasingly difficult. Difficulty level was monitored and set each day. Exercises trained emotion recognition by directing participants' attention to different aspects of an expression and providing verbal descriptions of distinguishing perceptual characteristics (e.g. closed mouth with lips pulled down slightly is characteristic of sadness). Participants then practiced identifying intense and subtle displays of that expression and identifying that target expression amongst other expressions. More complex emotion processing is trained through descriptions of situations that provoke each emotion and exercises that require the identification of emotional states and accompanying emotion-congruent dialogue in "real-world" social scenes. Correct responses were rewarded with verbal feedback (from the program), pleasant sounds, and visual animations. Both basic and complex (e.g. jealous, guilty) emotions were covered.

2.2.3. Computer game (CG) placebo

The purpose of the CG program was to control for general cognitive benefits of AT+SCT, staff contact, monetary payments, and all other auxiliary aspects of computer-based cognitive interventions. Participants rotated through 16 commercially available computer games¹ according to a defined schedule (Fisher et al., 2009). Games included solitaire, checkers, dominoes, hangman, visuospatial puzzles, pattern matching, and others. The games were enjoyable but cognitively 'non-specific' in that they were not designed to improve a specific cognitive skill.

2.2.4. Intervention details

AT+SCT participants completed approximately 60 min of AT and 5–15 min of SCT per day; CG participants completed approximately 60 min of computer games per day on a suggested schedule of 5 days a week for 10 weeks. There was no difference between groups in number of intervention hours (AT+SCT=47.27 (9.1);

CG=46.36 (6.7), $t(20)=0.27$, $p=0.79$). Participants completed training individually on the computer in the laboratory setting. If travel was difficult, they could complete the training at home ($N=2$ AT+SCT; $N=4$ CG, non-significant difference). Research assistants set up the training programs, monitored time, and recorded exercises completed each day. Participants who trained at home were called each week to monitor progress. Data from the training were downloaded weekly. Participants received nominal payment for participation; payment was contingent on participation and not performance.

2.2.5. fMRI task: Facial emotion recognition

The fMRI emotion recognition task was designed to assess neural response when correctly identifying the six basic emotional expressions. Because choosing an emotion label out of seven options (six emotions plus neutral) has numerous task demands that are not central to emotion recognition (e.g. managing seven response buttons, excessive reading time for emotion labels), the six emotions were divided into two sets. The first set (fMRI runs 1&2) consisted of angry, disgust, sad (ADS), and neutral expressions. The second set (fMRI runs 3&4) consisted of happy, surprise, fear (HSurF) and neutral expressions. The emotions were grouped according to similar perceptual features (e.g. happy, surprise and fear are all 'open-mouth' expressions), making emotion discrimination more challenging. Emotions were grouped according to perceptual features because SCT/METT–SETT trains emotion recognition by highlighting perceptual features that characterize each emotion. Thus, the task was designed to maximally engage this trained skill. For each run, participants knew the expressions that would be presented. One face was presented on each trial. Participants identified the emotion out of four options listed below the face (e.g. Anger, Disgust, Sad or Neutral). Each trial was 4 s followed by a 4- to 8-s jittered intertrial-interval (ITI). The trial started with a neutral face (800 ms), switched briefly to an emotional expression (400 ms), returning to a neutral expression with response options listed below (2800 ms). The trial structure, with the brief presentation of emotion, was similar to the SCT/SETT training exercises, but used different stimuli. The rationale was that an assessment task which closely resembles the training exercises is likely to engage the same neurocognitive processes used during training. Therefore, the similarity between task and training would increase confidence that observed neural activity changes are related to the SCT intervention. Brief presentations were also used to enhance task difficulty and prevent amygdala habituation (Breiter et al., 1996). On neutral trials, the neutral face was presented (1200 ms); then response options appeared below (2800 ms). There were 32 neutral trials and 30 trials of each emotion.

Face stimuli were from standard stimulus sets (Ekman and Matsumoto, 1993; Goelevena et al., 2008; Gur et al., 2002). Each person (identity) that was presented with an emotional expression was also presented with a neutral expression. Most faces were Caucasian, but other races were also represented to approximately match Bay area demographics. The same task was administered before and after the intervention.

2.3. fMRI acquisition and analysis

See Supplemental material for details regarding data acquisition and analysis.

Images were acquired at 4 T and analyzed with Statistical Parametric Mapping (SPM8). The goal was to identify neural activity during accurate emotion recognition. Therefore accurate and inaccurate trials were modeled separately, and neural activity for accurate trials is reported. Accurate trials from individual emotions in each set were combined for maximum statistical power. Each set had two conditions (emotion and neutral); fMRI runs 1&2: Angry, Disgust, Sad (ADS) and Neutral; fMRI runs 3&4: Happy, Surprise, Fear (HSurF) and Neutral. Contrast files were created for each condition versus baseline (e.g. ADS > baseline) and emotional versus neutral expressions (e.g. ADS > Neutral) at each time point (Pre-training and Post-training). 'Baseline' consisted of the period in between trials when participants viewed a white fixation-cross on black background.

Group (AT+SCT/CG) × Time (pre/post) interaction effects were investigated by entering pre-training and post-training contrasts into a flexible factorial model in SPM. Each SPM model had three factors: Subject, Group (AT+SCT/CG) and Time (Pre/Post). The 'Subject' factor controls for between-subject variation (e.g. age, medication, and gender) at each time point. Each model also included the interaction of Age × Time as a covariate of no interest. Thus, all Group × Time models control for the effect of age at pre- and post-time points as well as the effect of age on pre-to-post change in neural activity.

The number of accurate trials included in analyses (i.e. statistical power) did not differ between groups or between time points. The fMRI statistical threshold was $p < 0.005$ uncorrected, 10 voxel/80 mm extent. (This is a common threshold for studies with amygdala hypotheses; see Supplemental material.) If an interaction occurred in a hypothesized region, correction for multiple comparisons was conducted for each region (anatomically defined) using the small volume corrections (SVC) tool in SPM8. Because Group × Time models account for error variance associated with both groups and both time points as well as the influence of age on all effects, pair-wise comparisons within the SPM model are not valid, and separate t -tests of specific comparisons (e.g. AT+SCT vs. CG before training) cannot be interpreted as post-hoc tests of the Group × Time interaction. However, separate

¹ Games were from the following software programs: Hoyle Puzzle and Board Games (2003, Navarre Corporation, Encore Software, Inc.); After Dark Games (1998, Sierra On-Line, Inc., Berkeley Systems); 303 Game Collection: 203 Game Pack and 100+ Great Games–Volume II (2003, Antidote Entertainment, ValuSoft, Inc.).

t-tests of within-group and between-group comparisons provide information about independent effects of group and time. These *t*-tests were conducted and amygdala results reported in [Supplemental material](#).

Figures and correlational analyses use neural activity from the peak voxel of significant clusters in the Group \times Time interaction analysis. All measures of neural activity represent percent signal change over baseline. Bar-plots display Group \times Time analysis results, i.e. average neural activity for each group and each time point (adjusted for covariates, etc. in the model). In addition, each subject's individual level of neural activity (unadjusted) from the peak voxel was used to examine brain–behavior relationships. A neural activity difference score was calculated for each subject by subtracting neural activity at the pre-training scan from neural activity at the post-training scan. This change in activity (Post–Pre) was correlated with change in MSCEIT Perceiving Emotions (Post–Pre) and MATRICS Global Cognition (Post–Pre) using partial correlations controlling for age.

3. Results

3.1. Behavioral results

Group (AT+SCT/CG) \times Time (Pre/Post) interaction effects were investigated for all measures ([Table 1](#)). MSCEIT Perceiving Emotions showed the predicted interaction. Follow-up analyses confirmed that AT+SCT participants had a greater pre-to-post training improvement than CG participants. There were no intervention-related changes for daily functioning (QLS), global cognition (MATRICS), or behavioral performance on the fMRI task. These null findings are inconsistent with prior studies showing global cognition improvements after AT ([Fisher et al., 2009](#)), and are most likely due to the small sample size. Lack of improvement on the fMRI task was also surprising and indicates that distractions inherent in the scanner environment (e.g., noise) may have overpowered benefits from training.

3.2. fMRI results

fMRI analyses investigated the hypothesis that face emotion processing regions (amygdala, STC, SRC) would show a significant Group \times Time interaction. We expected that, relative to CG, AT+SCT participants would have a greater pre-to-post increase in neural activity during emotion recognition. Regions showing Group \times Time interactions are listed in [Table 2](#) and shown in [Figs. 1 and 2](#).

3.2.1. Angry, disgust, sad

Analysis of Group \times Time interaction effects in the expected direction showed a significant interaction in left precentral gyrus for the accurate recognition of angry, disgust, sad relative to baseline (ADS > baseline). There were no significant Group \times Time interactions for ADS > Neutral.

3.2.2. Happy, surprise, fear

Analysis of Group \times Time interaction effects in the expected direction for the accurate recognition of happy, surprise and fear (HSurf > baseline) revealed a significant interaction in bilateral amygdala, right putamen, and right MPFC. Correction for multiple comparisons was conducted in each region using small volume correction (SVC). The Group \times Time interaction for both the left and right amygdala was significant (FWE, $p < .05$) after correction for multiple comparisons. However, interaction effects in the putamen and MPFC were not significant after correcting for multiple comparisons. Neural activity from each region is plotted in [Figs. 1 and 2](#). There were no significant Group \times Time interaction effects for HSurf > Neutral.

3.3. Correlations between neural activity and behavior

Across all participants, pre-to-post neural activity increase in right amygdala, right putamen, and right MPFC when accurately identifying happy, surprise and fear (HSurf > baseline) predicted pre-to-post improvement on MSCEIT Perceiving Emotions. Among AT+SCT participants, the increase in right amygdala activity was significantly related to improvement in emotion perception. This brain–behavior relationship was trend-level for left amygdala and non-significant for MPFC and putamen. There were no significant correlations between neural activity and MSCEIT performance in the CG group (correlations in [Table 3](#)).

There were no significant correlations between pre-to-post change in neural activity and change in MATRICS Global Cognition across all participants or within each group. This suggests that observed intervention-related increases in neural activity are not related to general cognitive improvement (correlations in [supplemental Table 1](#)).

4. Discussion

This placebo-controlled study tested whether a cognitive remediation program that combined both auditory-based cognitive training plus social-cognitive training (AT+SCT) would influence the neural mechanisms supporting facial emotion recognition. In comparison to schizophrenia participants who engaged in computer games (CG) for an equal number of hours, schizophrenia participants who engaged in AT+SCT showed significant improvements in behavioral and neural measures of emotion perception. Results from the fMRI facial emotion recognition task showed the predicted group-by-time interaction in bilateral amygdala, right putamen, and right MPFC for the accurate recognition of happy, surprise, and fear expressions. Neural activity in all three regions increased to a greater degree after AT+SCT than after CG. AT+SCT was also related to behavioral improvement on MSCEIT Perceiving Emotions, a standardized test of emotion perception, which requires identification of multiple emotions subtly displayed in faces and scenes. Across all participants, intervention-related activity increase in each region was related to behavioral improvement in emotion perception (MSCEIT Perceiving Emotions). Among AT+SCT participants, right amygdala activity increase when accurately recognizing happy, surprise, and fear significantly predicted behavioral improvement in emotion perception. Neural activity increases in left amygdala, putamen, and MPFC were also positively correlated with behavioral improvement, among AT+SCT participants, but did not reach statistical significance. By contrast, the CG group had no significant, or even strongly positive, relationships between neural change and behavioral improvement in emotion perception.

These findings suggest that the training program, which combined exercises in auditory processing and auditory/verbal working memory with exercises in facial emotion recognition and basic theory of mind, improved functioning of the neurocognitive system supporting emotion recognition. Several features of the study substantiate this interpretation. First, using correct emotion recognition trials in the fMRI analysis increases confidence that observed neural activity is related to emotion recognition ability. This is noteworthy since most studies collapse across correct and incorrect trials, making it difficult to know whether observed activity is supporting, hindering, or unrelated to the neurocognitive skill under investigation. Second, the correlation between intervention-related neural activity increase and intervention-related behavioral improvement on the MSCEIT, an independent test of emotion perception with different task demands, further demonstrates that the increase in neural activity is related to

emotion recognition ability and not an epiphenomenon of the fMRI task, such as ability to manage distractions in the scanner or limited response time on the task. The correlation between neural activity and MSCEIT performance also indicates that the fMRI assessment of neural change has predictive value beyond the immediate experimental context in which it was measured. Finally, the fMRI task was similar to (though not the same as) emotion recognition exercises in the social-cognitive training program. The similarity between task and training increased the likelihood that, after daily practice on emotion recognition exercises, participants would engage those same cognitive processes during the fMRI task. While this limits information about the generalizability of training, it increases confidence that the fMRI data illustrate neural systems involved in the skill targeted during training—in this case, emotion recognition. Importantly, because emotion recognition skills predict performance on broader measures of functional outcome (Hooker and Park, 2002), the findings indicate that training programs which include emotion recognition could have long-term functional benefits for individuals with schizophrenia.

AT+SCT's influence on the amygdala was observed in response to happy, surprise, and fearful expressions. All three expressions communicate the presence of an emotionally salient stimulus, i.e. a potential threat, reward, or unexpected event. Amygdala response to these expressions mobilizes and/or directs resources, such as attention and arousal, to facilitate the detection and memory of salient information, such as threats and rewards, in the environment (Hooker et al., 2006, 2008; Pessoa and Adolphs, 2010). Research suggests that when the goal is to identify the emotional expression, as it was here, amygdala response facilitates emotion identification by directing attention to distinguishing characteristics of the expression, such as the wide-open eyes characteristic of fear (Adolphs, 2010). Our data indicate that AT+SCT may have stimulated and/or harnessed this amygdala response in service of accurate emotion recognition.

Intervention-related changes were also observed in the MPFC and putamen. Although both putamen and MPFC are involved in facial emotion recognition (Adolphs, 2009; Calder and Young,

2005), their functions are not fully understood. In addition, the group-by-time interaction effects in these regions were not significant after correction for multiple comparisons, so these results should be considered preliminary and interpreted with caution.

The current findings add to a small but growing literature on the neural effects of cognitive remediation in schizophrenia. To date, most studies focus on cognitive training of memory and attention, and show that neural activity increases in regions supporting working-memory and cognitive-control skills, such as the lateral prefrontal and anterior cingulate cortices, with greater neural activity increases associated with greater gains in working-memory performance (Haut et al., 2010; Wexler et al., 2000; Wykes et al., 2002). Only two fMRI studies report intervention effects on emotion recognition. One tested schizophrenia participants on a facial emotion recognition task before and after 12 45-min sessions of "Training of Affect Recognition (TAR)" and did not find training-related increases in the amygdala or other primary emotion-processing regions (Habel et al., 2010b). Previous behavioral studies indicate that TAR improves emotion recognition accuracy for schizophrenia participants (Wolwer et al., 2005; Kurtz and Richardson, 2012), so most likely the fMRI task and/or analysis methods were not sensitive enough to reveal neural effects in emotion-processing regions. For example, the fMRI task only included happy, sad, and neutral faces, and these emotions may not be a robust enough emotional probe. Nonetheless, a subsample from that study showed a correlation between increased postcentral gyrus activity (i.e. somatosensory-related cortex (SRC)) after TAR training and improvement on the fMRI emotion recognition task (Habel et al., 2010b). These findings are consistent with our previous study which showed that, compared to CG participants, AT+SCT participants had a greater pre-to-post increase in postcentral gyrus activity for facial emotion recognition versus object-color recognition, and the intervention-related increase in neural activity correlated with improvement in MSCEIT Perceiving Emotions (Hooker et al., 2012). Notably, despite variability in emotion-processing region showing an intervention effect, the current and two previous studies all found a correlation

Table 1

Results [Mean (SD)] for all pre and post behavioral assessments. The interaction of Group (AT+SCT versus CG) and Time (Pre versus Post training) was examined for all variables. Post-hoc comparisons were conducted on variables showing a significant interaction.

Behavioral assessment	AT+SCT Pre	AT+SCT Post	CG Pre	CG Post	Group × Time interaction
MSCEIT^{a,b}					
Perceiving emotions ^c	88.0 (31.9)	97.6(29.1)	94.1(15.4)	92.5(19.6)	$F(1,20)=4.3, p=0.05 \eta_p^2=0.18$
Within group	Pre vs. Post: $t(10)=2.7, p=0.02$		Pre vs. Post: $t(10)=0.38, p=0.82$		
Between group	AT+SCT vs. CG: Pre $t(20)=0.57, p=0.56$; Post $t(20)=0.48, p=0.64$				
QLS—Average score	3.2(1.0)	3.3(0.69)	3.2(1.0)	3.6(1.2)	ns
MATRICES global cognition (z-score)	-0.80(0.54)	-0.65(0.69)	-0.77(0.69)	-0.78(0.77)	ns
fMRI emotion recognition task—% percent correct					
Angry (A)	54 (25)	60 (23)	68 (18)	71 (25)	ns
Disgust (D)	42 (22)	52 (26)	55 (22)	55 (22)	ns
Sad (S)	64 (16)	56 (24)	64 (25)	64 (23)	ns
Neutral (Runs 1&2)	84 (24)	88 (23)	78 (25)	89 (22)	ns
ADS total	54 (18)	56 (22)	62 (19)	63 (21)	ns
Happy (H)	81 (28)	78 (33)	87 (18)	92 (10)	ns
Surprise (Sur)	69 (15)	65 (26)	82 (16)	81 (19)	ns
Fear (F)	59 (23)	61 (27)	62 (22)	66 (22)	ns
Neutral (Runs 3&4)	88 (22)	85 (27)	91 (13)	92 (16)	ns
HSurF total	70 (18)	68 (25)	77 (14)	80 (14)	ns
All Emotions (A,D,S,H,Sur,F)	61 (17)	62 (22)	69 (14)	70 (18)	ns

ns = Non-significant.

^a One participant in the CG group did not have pre MSCEIT data. This participant's post score was substituted for pre scores so that statistical power for the group analysis would not be lost.

^b MSCEIT scores are standardized. Population average = 100; standard deviation = 15.

^c Repeated Measures ANOVA with age as a covariate showed no main effect of age ($F=0.28, p=0.06$). However, the group × time interaction was no longer significant ($F=1.75, p=0.20$).

Table 2
Regions that show a significant interaction of Group (AT+SCT/CG) and Time (Pre/Post Training). (A) Group \times Time interactions in the expected direction [i.e. AT+SCT versus CG showed an increase in activity from pre to post training]. Effect sizes for interaction effects in hypothesized regions are reported in the legend. Multiple comparisons are corrected for within each hypothesized region (anatomically defined) by applying the small volume correction (SVC) tool in SPM8, and significant results ($p < 0.05$ with Family Wise Error correction) are designated with an asterisks (*). (B) Group \times Time interactions in the unexpected direction [i.e. AT+SCT versus CG showed a decrease in activity from pre to post training].

Anatomical region	R/L	BA	Cluster volume in voxels/mm ³	x	y	z ^Ω	T value ^β	p value ^ω	F value ^κ
(A) Group \times Time interaction in the expected direction: AT+SCT vs. CG showed an increase in activity from pre to post									
Facial emotion recognition task									
Happy, surprise, fear vs. baseline									
Amygdala* ^a	L	34	41/328	-16	4	-20	4.35	0.000	17.22
Putamen [⊗]	R	-	67/536	26	-4	0	3.86	0.001	14.88
Superior frontal Gyrus–medial (MPFC) [⊗]	R	10	14/112	12	60	4	3.45	0.001	11.89
Nucleus basalis	R	-	13/104	-10	-2	-6	3.40	0.002	11.55
Amygdala ^{*b}	R	34	32/256	24	6	-16	3.28	0.002	10.75
Gyrus rectus/medial orbitofrontal cortex	R	11	43/344	6	20	-20	3.21	0.002	10.29
Angry, sad, disgust vs. baseline									
Precentral gyrus	L	6	51/408	-4	-2	72	3.79	0.001	14.34
(B) Group \times Time interaction in the unexpected direction: AT+SCT vs. CG showed a decrease in activity from pre to post									
Facial emotion recognition task									
Happy, surprise, fear vs. baseline									
Thalamus–Pulvinar cluster extends bilaterally	L	-	92/736	-6	-20	6	4.23	0.000	17.91
Middle frontal gyrus	R	-	45, 46	6	-22	6	3.45	0.001	11.94
				-48	36	34	3.99	0.000	13.98
Angry, sad, disgust vs. baseline									
No significant findings									

^β Critical T value ($p < 0.005$) is $t(19) = 2.86$.

^ω p value for corresponding t value.

^κ Critical F value ($p < 0.005$) is $F(1, 19) = 10.07$.

^Ω x, y, z coordinates of peak voxel are in Montreal Neurological Institute (MNI) template space.

^{*} Survives correction for multiple comparisons [Family Wise Error (FWE), $p < 0.05$] within the amygdala (anatomically defined) using small volume correction (SVC) in SPM8.

[⊗] SVC within the right putamen, FWE, $p = 0.07$; SVC within the MPFC (anatomical region which combined anterior cingulate cortex and medial portion of the superior frontal gyrus) FWE, $p = 0.26$.

^a Effect size $d = 1.90$; ^b Effect Size $d = 1.51$.

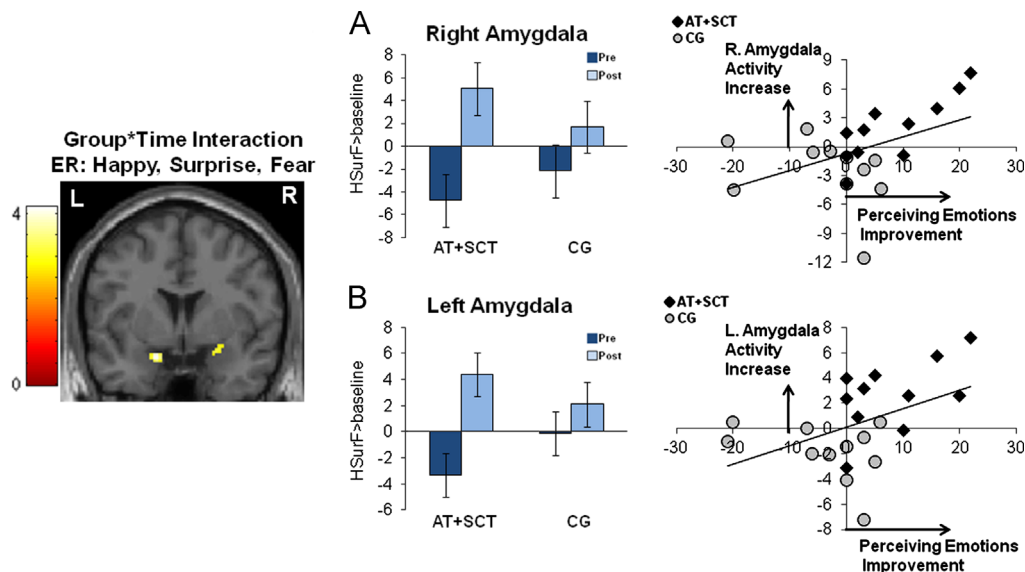


Fig. 1. Group \times Time interaction effects for emotion recognition (ER) of Happy, Surprise, Fear (HSurF). Color scale represents t -values. (A) right amygdala; and (B) left amygdala. Bar plots show amygdala activity (percent signal change) of the contrast HSurF $>$ baseline for each group and time point. Scatter plots show correlations between change in amygdala activity (Post–Pre) and change in MSCEIT Perceiving Emotions (Post–Pre) across all participants. The correlation between neural activity increase and behavioral improvement was significant in right amygdala, $r = 0.45$, $p < 0.05$ and a trend in left amygdala, $r = 0.39$, $p < 0.10$.

between increased neural activity and improvement in emotion recognition skills. Collectively, these findings indicate not only that the neurocognitive system supporting emotion recognition is responsive to behavioral intervention, but also that detection of intervention-related effects is influenced by design elements of the neuroimaging assessment. While all regions in the network, particularly the amygdala, STC, and SRC, are involved in emotion

recognition, each region may be maximally responsive to different emotions or different aspects of emotion processing. For example, the amygdala tends to show greater response to fearful expressions than other expressions and the STC tends to show greater response to dynamic than static facial features. Thus, aspects of task design, such as emotion type and/or response judgment, can bias detection of intervention effects in one region over another.

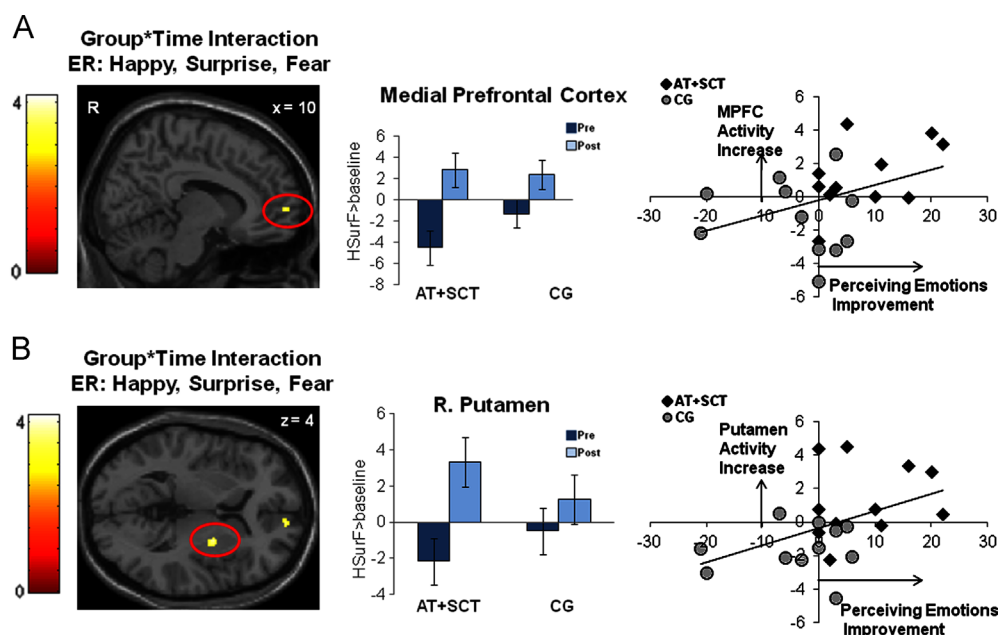


Fig. 2. Group \times Time interaction effects for emotion recognition (ER) of Happy, Surprise, Fear (HSuF). Color scale represents t -values. (A) right medial prefrontal cortex (MPFC); and (B) right putamen. Bar plots show neural activity (percent signal change) for contrast HSurF > baseline for each group and time point. Scatter plots show correlations between change in neural activity (Post–Pre) and change in MSCEIT Perceiving Emotions (Post–Pre) across all participants. The correlation between neural activity increase and behavioral improvement was significant for both the putamen, $r=0.44$, $p < 0.05$ and MPFC, $r=0.43$, $p=0.05$.

Table 3

Correlation coefficients for the relationship between change in neural activity (i.e. difference in activity: Post–Pre) and change in MSCEIT Perceiving Emotions subscale score (Post–Pre). A positive correlation indicates that an increase in neural activity is related to behavioral improvement in MSCEIT Perceiving Emotions score. All correlations are controlling for the effect of age.

	All participants, $N=22$	AT+SCT, $N=11$	CG, $N=11$
Neural activity change for emotion recognition of happy, surprise, fear correlated with change in MSCEIT perceiving emotions			
Left amygdala (–16, 4, –20)	0.39 [#]	0.59 [#]	–0.44
Right amygdala (24, 6, –16)	0.45 [*]	0.84 [*]	–0.38
Right putamen (26, –4, 0)	0.44 [*]	0.25	0.17
Medial prefrontal cortex (12, 60, 4)	0.43 [*]	0.53	–0.19

*Correlation is significant at $p < 0.05$ level (2-tailed).

[#]Correlation is significant at $p < 0.10$ level (2-tailed).

Nonetheless, recent results from structural neuroimaging provide converging evidence of neuroplasticity in the amygdala and other social-cognitive regions. Schizophrenia participants who completed 2 years of Cognitive Enhancement Therapy (CET), which combines computerized cognitive remediation and group-based social skills training, showed an increase in amygdala gray matter volume and less gray matter decline in other regions, and intervention-related neural changes predicted behavioral improvement on the MSCEIT composite score (Eack et al., 2010).

One limitation of our study is the inability to determine whether neural changes in emotion-processing regions result from the combination of cognition and social-cognition training or whether social-cognition training that exclusively targets emotion recognition would produce these changes. In addition, the neural changes observed during emotion recognition did not factor out neural response to neutral faces (i.e. there was no group-by-time interaction for the emotion vs. neutral contrast), so the current results may partially reflect a general improvement in face processing. Another limitation is the small and heterogeneous sample. AT+SCT participants were older, on average, than CG participants, and across the entire sample, individuals varied in illness duration, symptom profile, and medication type. Although we controlled for age in our analyses, more homogeneous samples

and closely matched groups will provide a clearer picture of cognitive training effects. Due, in part, to the immense resources required for this type of research, nearly all published studies on neural effects of cognitive training have small sample sizes (Haut et al., 2010; Wexler et al., 2000; Wykes et al., 2002). While these studies, including our own, provide important preliminary evidence, larger samples may reveal more robust between-group results and more individual variation that can inform brain-behavior relationships. In contrast to previous findings (Fisher et al., 2009), AT+SCT, in this study, was not associated with improved global cognition. Neuroimaging studies with larger samples would be more likely to replicate behavioral effects of validated interventions. We also did not find intervention-related improvement in daily functioning or a relationship between neural change and functional improvement. However, functioning was assessed immediately after training, which was probably not enough time for training effects to yield functional improvement. A previous study with combined cognitive and social cognitive training found that a relationship between training-induced neural change and functioning is only apparent 6 months after the intervention (Subramaniam et al., 2012).

In summary, the emerging data indicate that well-designed behavioral training interventions can improve neural system

functioning in schizophrenia; the next challenge is to translate these findings into therapeutic strategies that help individuals with the illness lead maximally fulfilling and socially engaged lives.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.psychres.2013.04.001>.

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