



Neural activity during emotion recognition after combined cognitive plus social cognitive training in schizophrenia

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ABSTRACT

Cognitive remediation training has been shown to improve both cognitive and social cognitive deficits in people with schizophrenia, but the mechanisms that support this behavioral improvement are largely unknown. One hypothesis is that intensive behavioral training in cognition and/or social cognition restores the underlying neural mechanisms that support targeted skills. However, there is little research on the neural effects of cognitive remediation training. This study investigated whether a 50 h (10-week) remediation intervention which included both cognitive and social cognitive training would influence neural function in regions that support social cognition. Twenty-two stable, outpatient schizophrenia participants were randomized to a treatment condition consisting of auditory-based cognitive training (AT) [Brain Fitness Program/auditory module ~60 min/day] plus social cognition training (SCT) which was focused on emotion recognition [~5–15 min per day] or a placebo condition of non-specific computer games (CG) for an equal amount of time. Pre and post intervention assessments included an fMRI task of positive and negative facial emotion recognition, and standard behavioral assessments of cognition, emotion processing, and functional outcome. There were no significant intervention-related improvements in general cognition or functional outcome. fMRI results showed the predicted group-by-time interaction. Specifically, in comparison to CG, AT + SCT participants had a greater pre-to-post intervention increase in postcentral gyrus activity during emotion recognition of both positive and negative emotions. Furthermore, among all participants, the increase in postcentral gyrus activity predicted behavioral improvement on a standardized test of emotion processing (MSCEIT: Perceiving Emotions). Results indicate that combined cognition and social cognition training impacts neural mechanisms that support social cognition skills.

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1. Introduction

Cognitive remediation research indicates that people with schizophrenia can improve their cognitive and social cognitive skills after targeted behavioral training (Wykes et al., 2011). Because cognitive and social cognitive deficits are associated with poor functional outcome (Green, 2007) and are not substantially improved with pharmacological treatment (Keefe et al., 2007; Swartz et al., 2007), cognitive remediation holds tremendous promise as a functionally beneficial treatment for schizophrenia. To maximize these benefits, it is imperative to understand how cognitive training contributes to behavioral improvement. Because cognitive and social cognitive behavioral impairments in schizophrenia arise from abnormalities in neural circuitry

(Aleman and Kahn, 2005; Barch, 2005), it is often assumed that cognitive training facilitates behavioral improvement through learning-induced neuroplasticity, a process in which behavioral training induces beneficial neural changes, such as neuronal tuning and cortical expansion, that result in better cognitive processing (Ohl and Scheich, 2005; Polley et al., 2006). However, this assumption is rarely tested, and neural effects of cognitive remediation in schizophrenia are largely unknown.

The purpose of this study was to identify whether a cognitive remediation intervention which targeted both cognitive and social cognitive skills would induce beneficial neural changes in regions that support social cognition. Thus far, most cognitive remediation studies have focused on cognitive skills, such as attention and memory (Wykes et al., 2011). While there is no doubt that cognitive skills must be included in any comprehensive cognitive remediation intervention for schizophrenia, there is overwhelming evidence that social cognitive skills must also be addressed. Social cognitive skills, such as facial emotion recognition, are severely impaired in schizophrenia and significantly

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predict functional outcome, even after accounting for the contribution of general cognition (Hooker and Park, 2002).

In this project, social cognitive training and pre/post assessments focused on facial emotion recognition. This choice was motivated by several factors. First, neural regions that process facial emotion are clearly defined and dissociable from regions that process non-emotional information from visual stimuli, such as the physical properties of objects and faces. Regions involved in facial emotion recognition include the amygdala, superior temporal cortices (STC), and somatosensory-related cortices (SRC), particularly the postcentral gyrus. Among non-psychiatric individuals, these regions are more active during face emotion recognition than face identity recognition and lesions produce deficits in emotion recognition but not identity recognition (Adolphs et al., 2000; Adolphs et al., 2003; Pitcher et al., 2008). Second, people with schizophrenia have facial emotion recognition deficits that are related to both functional outcome (Hooker and Park, 2002) and neural abnormalities (Namiki et al., 2007). Finally, facial emotion recognition training in people with schizophrenia leads to behavioral improvement in facial emotion recognition skills (Kurtz and Richardson, 2011).

The combined cognitive plus social cognitive training program used here builds on our previous research. Schizophrenia participants who completed cognitive (auditory-based) training focused on verbal learning and memory showed significant improvements in cognition but not social cognition (Fisher et al., 2009), whereas schizophrenia participants who completed auditory-based cognitive training plus social cognitive training showed improvement in both cognition and social cognition, including facial emotion recognition (Sacks et al., *in press*). Here, we investigate the influence of this cognitive plus social cognitive training on neural activity during facial emotion recognition.

Schizophrenia participants were randomized to the treatment [auditory-based training (AT) plus social cognitive training (SCT)] or placebo [computer-games (CG)] intervention. Participants completed an fMRI facial emotion recognition task, behavioral cognition and social cognition tests, and assessments of functioning before and after the 50 h computer-based intervention. Primary hypotheses were that cognitive plus social cognitive training (AT + SCT) would result in greater activity in the amygdala, STC, and/or SRC during facial emotion recognition, and this increase in activity would predict behavioral improvement on an independent measure of emotion perception.

A secondary goal was to investigate intervention-related neural change for the recognition of positive emotions. Positive social signals are inherently rewarding. In healthy individuals, the ventral striatum (VS) and other reward-processing regions are active in response to positive social signals, such as direct gaze from a smiling and/or attractive person (O'Doherty et al., 2003; Spreckelmeyer et al., 2009). Schizophrenia is associated with behavioral deficits in the experience, expression, and recognition of positive emotions (Horan et al., 2008; Tsoi et al., 2008; Cohen and Minor, 2010; Cohen et al., 2011), as well as reduced VS activity in anticipation of monetary reward (Juckel et al., 2006). Together these findings suggest that deficient neural response to positive social signals could contribute to socially relevant features of illness, such as social anhedonia and poor social initiative. However, research on this potential brain-behavior relationship is limited. Most fMRI emotion recognition studies focus on negative emotions. If positive emotions are included, it is usually only happy expressions, and the task is not designed to investigate neural correlates of positive expressions specifically. Our fMRI task included the blocked presentation of four positive (happy, dreamy, flirty, happily surprised) and four negative (anger, disgust, fear, sad) expressions. The project's overarching hypothesis was that neural response for all facial expressions would increase after AT + SCT. Thus for positive expressions, we expected VS activity to increase after AT + SCT.

2. Methods

2.1. Participants and assessments

Participants were $n=22$ volunteers with schizophrenia or schizoaffective disorder ($n=11$ AT + SCT and $n=11$ CG). This study ran in parallel with our larger randomized controlled trial of cognitive training in schizophrenia (ClinicalTrials.gov NCT00312962). Participants were outpatients and had no significant medication changes during the study. After procedures were explained, participants gave written informed consent and underwent baseline assessments over 4–5 weeks.

Diagnosis was assessed with Structured Clinical Interview for DSM-IV Disorders, medical records, and caretaker reports. Behavioral assessments included Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) for IQ (baseline); Positive and Negative Syndrome Scale-Extended (PANSS-E) for symptom severity; Quality of Life Scale-Abbreviated (QLS) (Bilker et al., 2003) for functioning; Global Cognition computed from MATRICS-recommended measures (Nuechterlein et al., 2008) for cognitive performance; and Mayer-Salovey-Caruso-Emotional Intelligence Test (MSCEIT) Perceiving Emotions subscale (Mayer et al., 2003) for emotion perception. In MSCEIT Perceiving Emotions, participants viewed pictures of faces, paintings, and landscapes (10 trials) and rated the extent (1–5 scale) that five designated emotions were expressed in the picture.

Diagnosis, PANSS-E, and QLS ratings were reached by consensus between two raters ($ICC > .85$). Research staff who randomized subjects did not conduct assessments; assessment staff were blind to group assignment. Inclusion criteria: schizophrenia or schizoaffective disorder, age 18–60 years, and primary English-speaker. Exclusion criteria: head trauma history, $IQ < 70$, neurological or major medical illness, or substance dependence within 6 months. After baseline testing, participants were stratified by age, education, gender, and symptom severity and randomly assigned to AT + SCT or CG. Participant characteristics are reported in Table 1.

2.2. Intervention

2.2.1. Auditory training (AT)

The AT program was developed by Posit Science Corporation (<http://www.positscience.com>) and described elsewhere (Fisher et al., 2009). Briefly, the program consisted of computerized exercises designed to improve auditory and verbal information processing. Participants made progressively more difficult distinctions about auditory stimuli and speech under conditions of increasing working memory load. Exercises became more complex, requiring participants to incorporate their improvements in auditory perception into higher-level cognitive skills, such as verbal learning and memory. Difficulty level was continuously adjusted to maintain ~80% accuracy.

2.2.2. Social cognition training (SCT)

The SCT program consisted 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 techniques were similar to AT in that exercises engaged both perceptual and executive control processes with progressive difficulty. Each training session covered 1–4 emotion(s), and focused on facial expressions. Difficulty level was monitored and set each day. Exercises directed participants' attention to distinguishing perceptual characteristics of specific emotions (e.g. furrowed brow is characteristic of anger). Participants then identified increasingly subtle displays of that expression and distinguished that expression from others. Exercises progressively trained more sophisticated emotion processing by requiring participants to identify situations that would provoke each emotion and to match emotional expressions with 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 emotions were covered.¹

2.2.3. Computer game (CG) placebo

The CG placebo was designed to control for non-specific cognitive components of AT + SCT, and all other auxiliary aspects of computer-based cognitive interventions, including staff contact and monetary payments. Participants rotated through 16 commercially available computer games according to a set schedule (Fisher et al., 2009). Selected games were engaging but ‘non-specific’ (i.e. not targeting cognitive improvement). Games included visuospatial puzzles, solitaire, checkers, and similar others.

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 a day. The suggested schedule for both groups was 5 days/week for 10 weeks. There were no between-group differences in number of intervention hours (AT + SCT = 47.27(9.1); CG = 46.36(6.7), $t(20) = .27$, $p = .79$). Participants completed training in the laboratory setting or at home ($n = 2$ AT + SCT; $n = 4$ CG, non-significant difference) if travel was difficult. Payment was contingent on participation not performance. University of California, San Francisco and Berkeley ethical review boards approved the study.

2.3. fMRI emotion recognition task

Participants completed a blocked-design emotion recognition task with three conditions: Recognition of Negative Emotions (anger, disgust, fear, sad); Positive Emotions (dreamy, flirty, happy, happily surprised); and Object-color (blue, red, white, yellow). Object-color was the baseline condition rather than neutral faces or non-emotional judgments in order to avoid experimental confounds. Schizophrenia participants have abnormally high activity in emotion-processing regions to neutral faces (Holt et al., 2006) and non-emotional (e.g. age) judgments of emotional faces require inhibiting emotional information, which is a deficit in schizophrenia (Barch, 2005).

Each block contained eight, 4 s trials followed by a 12 s fixation-cross/rest period. On each trial, a picture appeared (face or object) with the four response options below (e.g. “anger, disgust, fear, sad” for Negative Emotion blocks). Each condition block was presented 6 times across two fMRI runs. Stimuli were from standard stimulus sets and were different than training stimuli.

2.4. fMRI data acquisition and analysis

See Supplemental Materials for detailed description.

Images were acquired at 4T and analyzed with SPM8. Single-subject models included three conditions: Negative Emotions; Positive Emotions; Objects. Three contrasts were created for each time-point (pre/post): Negative > Objects; Positive > Objects; Positive > Negative. These pre and post contrasts were entered into separate ANOVA models to investigate Group*Time interactions while controlling for age. Statistical threshold was $p < .001$ (uncorrected), cluster extent 10 voxels/80 mm. If interactions occurred in hypothesized regions, multiple comparison correction was conducted within the anatomical region using Small Volume Correction (FWE, $p < .05$), and neural data was extracted from the cluster. This extracted data was used for correlations between neural change and behavioral change. Brain-behavior correlations used the

¹ Emotions that were specifically trained included happy, sad, angry, fear, disgust, surprise, contempt, excited, interested, thinking, liking, mean, shy, hurt, bored, wanting, jealous, sorry, guilty, liked.

Table 1
Participant characteristics.

	AT + SCT	CG
Gender: (F/M)	1 F/10 M	3 F/8 M
Age: mean (SD)*	51.2 (5.8)	41.0 (8.4)
Education: mean (SD)	13.7 (2.2)	12.8 (2.5)
WASI Full Scale IQ: mean (SD)	98.2 (18.7)	103.6 (19.4)
Vocabulary T score	53.3 (10.3)	54 (13.8)
Matrix Reasoning T score	50.1 (12.6)	48.8 (13.0)
Diagnosis (n)		
Schizophrenia	6	7
Schizoaffective	5	4
Length of illness: mean (SD)	28.0 (8.3)	20.6 (11.6)
Chlorpromazine equivalent: mean (SD)	252.5 (339)	371.4 (456)
Other medications: mood stabilizers, SSRIs, or benzodiazepines (n)	5	5
PANSS total score: mean (SD)	76.2 (15.4)	68.1 (16.3)

* The AT + SCT group was significantly older than the CG group: $t(20) = 3.3$, $p < .05$. There were no other significant differences between the groups.

MSCEIT because performance was independent from the task that elicited brain activity.

3. Results

3.1. Behavioral results

Group(AT + SCT/CG)*Time(pre/post) interaction effects were investigated for all behavioral measures (Table 2). MSCEIT Perceiving Emotions showed a significant interaction; AT + SCT improved more than CG participants. When controlling for age, the Group*Time interaction was no longer significant. Specific effects of age are not clear. CG participants had non-significantly higher scores than AT + SCT at baseline and a non-significant pre-to-post decline. This pattern may have contributed to the interaction and could reflect CG participants' younger age. There were no intervention effects on functional status (QLS). There were no significant effects for global cognition which is inconsistent with prior reports (Fisher et al., 2009) and likely due to small sample size.

Behavioral performance on the fMRI task showed a significant Group*Time interaction for the recognition of positive emotions; AT + SCT improved more than CG participants. There was no Group*Time interaction for negative emotions or object-color. Null results for negative emotions were surprising; however, lower accuracy suggests they were harder than positive emotions, perhaps causing greater susceptibility to distraction-related errors, which would obscure intervention-related improvements.

3.2. fMRI results

3.2.1. Group*Time interactions: Expected direction

Results from the Group*Time analysis of Negative Emotions > Objects showed a significant interaction in the expected direction (i.e. intervention-related increase for AT + SCT versus CG) in right postcentral gyrus, a hypothesized region involved in facial emotion recognition. Results for Positive > Objects also revealed a Group*Time interaction in right postcentral gyrus. In both contrasts, the interaction remained significant after correction for multiple comparisons.

Results for Positive > Negative Emotions showed Group*Time interaction effects in VS, specifically globus pallidus. Interaction effects for Positive > Negative Emotions were also observed in precentral and superior frontal gyri. There were no Group*Time interactions for Negative > Positive Emotions. See Figs. 1–3 and Table 3.

3.2.2. Group*Time interactions: Unexpected direction

There was a Group*Time interaction in the unexpected direction (i.e. intervention-related decrease for AT + SCT versus CG) for Negative > Objects in gyrus rectus and medial superior frontal gyrus.

Table 2
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*Session interaction
MSCEIT* ^a					
Perceiving emotions ^a	88.0 (31.9)	97.6(29.1)	94.1 (15.4)	92.5 (19.6)	$F(1,20) = 4.3, p = .05$ $\eta^2_p = .18$
Within group	Pre vs. Post: $t(10) = 2.7, p = .02$		Pre vs. Post: $t(10) = .38, p = .82$		
Between group	AT + SCT vs. CG: Pre $t(20) = .57, p = .56$; Post $t(20) = .48, p = .64$				
QIS–average score	3.2 (1.0)	3.3 (.69)	3.2 (1.0)	3.6 (1.2)	ns
MATRICS global cognition (z-score)	-.80 (.54)	-.65 (.69)	-.77 (.69)	-.78 (.77)	ns
fMRI emotion recognition task* (proportion correct)					
Negative emotions	.65 (.15)	.71 (.16)	.72 (.13)	.73 (.15)	ns
Positive emotions ^b	.72 (.14)	.81 (.10)	.76 (.07)	.73 (.15)	$F(1,20) = 7.44, p = .01$ $\eta^2_p = .27$
Within group	Pre vs. Post: $t(10) = 2.64, p = .03$		Pre vs. Post: $t(10) = 1.1, p = .30$		
Between group	AT + SCT vs. CG: Pre $t(20) = .88, p = .39$; Post $t(20) = 1.4, p = .18$				
Object-color	.95 (.10)	.96 (.04)	.97 (.04)	.95 (.09)	ns

ns = non significant.

* 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.

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

^a Repeated measures ANOVA with age as a covariate showed no main effect of age ($F = .28, p = .6$). However, the group*time interaction was no longer significant ($F = 1.75, p = .20$).

^b One participant in the CG group did not have post behavioral data from the fMRI task. The participant's pre score for the fMRI task was substituted for this participant's post score so that statistical power for the group analysis would not be lost.

^b Repeated Measures ANOVA with age as a covariate showed no effect of age ($F = .04, p = .85$), and the group*time interaction remained significant ($F = 5.09, p = .04, \eta^2_p = .21$).

There were no significant findings in the unexpected direction for Positive > Objects (Table 4).

3.3. Correlation between neural change and behavioral change

Across all participants, change in right postcentral gyrus activity when recognizing both negative (Negative > Objects) and positive (Positive > Objects) emotions was significantly correlated with change in MSCEIT Perceiving Emotions score (Figs. 1–3, Table 5).

Table 3

Regions across the whole brain that show a significant interaction of Group (AT + SCT/CG) and Time (Pre/Post Training) in the expected direction [i.e. AT + SCT versus CG showed an increase in activity from pre to post training]. If a Group*Time interaction is detected in a hypothesized region, multiple comparisons are corrected for within the anatomical region (significant results are noted with *) and the effect size is calculated and reported in the legend.

Anatomical region	R/L	BA	Volume in voxels (mm)	MNI x, y, z coordinates	T value
Negative emotions vs. objects					
Postcentral gyrus* ^a	R	3	15 (120)	42 – 20 44	4.58
Positive emotions vs. objects					
Supplementary motor area	R	6	23 (184)	10 – 12 58	4.40
Precentral gyrus	R	4	18 (144)	34 – 16 58	4.33
Precentral gyrus	L	4	24 (192)	– 14 – 22 56	4.20
Postcentral gyrus* ^b	R	3	35 (280)	42 – 20 44	4.12
Superior temporal gyrus/Heschl's gyrus ^c	R	48	17 (136)	48 – 12 8	3.97
Angular gyrus	L	39	11 (88)	– 44 – 58 42	3.84
Positive emotions vs. negative emotions					
Superior frontal gyrus	R	9	15 (120)	38 8 56	5.05
Ventral striatum (globus pallidus)* ^d	R	N/A	14 (112)	20 4 0	4.25
Precentral gyrus	L	6	23 (184)	– 44 0 24	4.16
Precentral gyrus	L	6	17 (136)	– 44 2 38	3.91
Negative emotions vs. positive emotions					
No significant findings					

^aEffect size $d = 2.10$; ^bEffect size $d = 1.89$; ^cEffect size $d = 1.82$; ^dEffect size $d = 1.95$.

Note: Additional inspection indicated Group*Time interaction effects for Negative > Object and Positive > Object in left postcentral gyrus that were just below statistical threshold. This suggests that the observed effect in right postcentral gyrus is not completely right lateralized.

* Survives correction for multiple comparisons within the anatomical region. Postcentral gyrus, globus pallidus, and superior temporal gyrus were examined with SVC.

Greater increase in postcentral gyrus activity predicted greater improvement in emotion perception.

Additionally, across all participants, activity increase in left angular gyrus for Positive > Objects and left precentral gyrus for Positive > Negative significantly correlated with MSCEIT Perceiving Emotions improvement.

4. Discussion

This study examined the influence of combined cognitive (auditory-based) training plus social cognitive training (AT + SCT) on neural mechanisms supporting emotion recognition. Compared to schizophrenia participants who completed 50 h of computer games (CG), schizophrenia participants who completed 50 h of AT + SCT showed improvement in both behavioral and neural measures of emotion recognition. First, fMRI results showed the predicted group by time interaction in the right postcentral gyrus, a neural region known to support facial emotion recognition (Adolphs et al., 2000; Pitcher et al., 2008). AT + SCT, relative to CG participants, had a greater pre-to-post intervention increase in right postcentral gyrus activity when recognizing both positive and negative facial expressions. Second, AT + SCT participants showed more behavioral improvement on MSCEIT Perceiving Emotions, a standardized test of emotion perception in faces and scenes administered outside of the scanner. Third, across all participants, the increase in right postcentral gyrus activity for both positive and negative expressions predicted behavioral improvement in MSCEIT Perceiving Emotion scores.

These findings suggest that AT + SCT, which includes training in emotion recognition, improved function in a neural structure necessary for emotion recognition skills. Disruption of postcentral gyrus activity, either from temporary inactivity or permanent damage, causes deficits in facial emotion recognition but not other aspects of face processing (Adolphs et al., 2000; Pitcher et al., 2008). Because the postcentral gyrus mediates somatosensory experience, one interpretation is that postcentral gyrus activity facilitates emotion recognition through simulation, a process in which people understand the feelings of others by generating that feeling in themselves. Although this study cannot identify whether participants used simulation, future studies could investigate this possibility.

Additionally, the results offer partial evidence that AT + SCT engaged reward-related processing in the ventral striatum (VS) in response to positive facial expressions. Compared to CG, AT + SCT participants had an intervention-related increase in VS activity for positive (versus

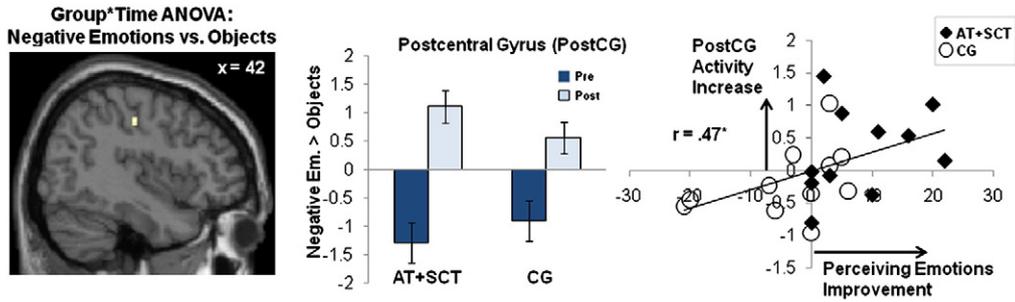


Fig. 1. Group*Time interaction effects in the expected direction (i.e. AT + SCT have greater activity post vs. pre training) for recognition of negative emotions as compared to recognition of object color (Contrast: Negative Emotions> Objects). There was a significant interaction in right postcentral gyrus (peak voxel x, y, z coordinates: 42, -20, 44). The bar plot shows neural activity (percent signal change) for the contrast Negative Emotions> Objects for each group at each time point. The scatter plot shows the correlation between the change in neural activity (Post activity minus Pre activity) with the change in MSCEIT Perceiving Emotions score (Post score minus Pre score) across all participants.

negative) emotions. AT + SCT participants also showed a pre-to-post intervention increase in precentral gyrus activity for positive (versus negative) emotions, and this increase was related to behavioral improvement in MSCEIT Perceiving Emotions. These findings for positive versus negative emotions are intriguing; however they require further investigation because positive emotions included three complex emotions that were not specifically trained, whereas negative emotions included basic emotions that were specifically trained.

Given these differences, it is noteworthy that intervention-related effects in the postcentral gyrus were nearly identical for positive and negative emotions relative to objects and not significantly different when positive and negative emotions were directly compared. This is consistent with research showing that postcentral gyrus activity contributes to the recognition of both positive and negative emotions and suggests that AT + SCT helped restore this function.

Overall, the neural changes demonstrated here provide initial evidence of learning-induced neuroplasticity in schizophrenia. The findings substantiate prior data showing that among schizophrenia participants, cognitive training in working-memory leads to an increase in dorsolateral prefrontal cortex activity which is associated with improved working-memory (Wexler et al., 2000; Wykes et al., 2002; Edwards et

al., 2010; Haut et al., 2010). The only other study to examine neural effects of facial emotion recognition training found relatively weak results; occipital cortex and inferior frontal gyrus showed intervention-related increases during facial emotion recognition, but there were no significant changes in primary emotion recognition regions (Habel et al., 2010). However, the fMRI task only included three expressions (happy, sad, neutral), which may not have been robust enough to reveal intervention-related effects. Even so, in a subsample of participants, intervention-related increase in postcentral gyrus activity correlated with behavioral improvement on the fMRI emotion recognition task, which is consistent with results presented here.

The current study has several limitations. First, because the design combined cognitive and social cognitive training, it is impossible to know whether social cognition or the combination of cognition and social cognition training produced the results. Second, our sample size was small, mostly male, and included participants with a wide range of age, illness duration, and symptom profiles. These demographic factors could have different influences on training response, and the heterogeneity probably reduced the ability to reveal training-related improvements. For example, men, at baseline, have less accurate facial emotion recognition than women (Thayer and Johnsen, 2000), raising the possibility that

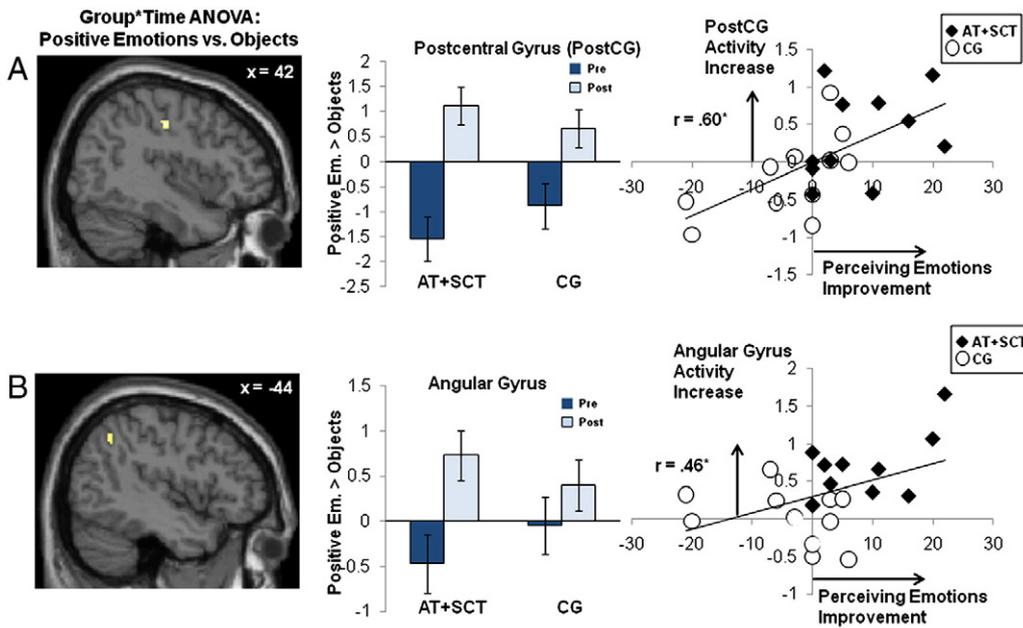


Fig. 2. Group*Time interaction effects in the expected direction (i.e. AT + SCT have greater activity post vs. pre training) for recognition of positive emotions as compared to recognition of object color (Contrast: Positive Emotions> Objects). (A) Right postcentral gyrus [peak voxel x, y, z coordinates: 42, -20, 44]. (B) Left angular gyrus [peak voxel x, y, z coordinates: -44, -58, 42]. For each region, the bar plot shows neural activity (percent signal change) for the contrast Positive Emotions> Objects for each group at each time point. The scatter plot shows the correlation between the change in neural activity (Post activity minus Pre activity) with the change in MSCEIT Perceiving Emotions score (Post score minus Pre score) across all participants. Note: In (B) two people in AT + SCT group have zero change on MSCEIT and approximately the same level of brain activity, so the two diamond symbols are overlapping and only 10 diamonds are visible.

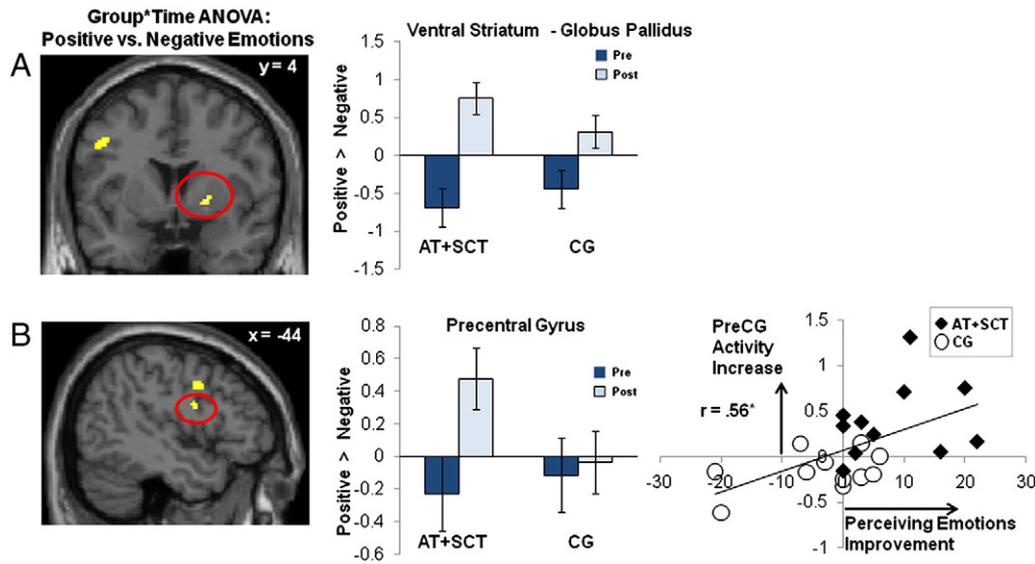


Fig. 3. Group*Time interaction effects in the expected direction (i.e. AT + SCT have greater activity post vs. pre training) for recognition of positive emotions as compared to recognition of negative emotions (Contrast: Positive Emotions > Negative Emotions). (A) Right ventral striatum with peak in globus pallidus [peak voxel x, y, z coordinates: 20, 4, 0]. The bar plot shows neural activity (percent signal change) for the contrast Positive Emotions > Negative Emotions for each group at each time point. There was no significant correlation between change in ventral striatum activity and change in MSCEIT Perceiving Emotions score. (B) Left precentral gyrus [peak voxel x, y, z coordinates: -44, 0, 24]. The bar plot shows neural activity (percent signal change) for the contrast Positive Emotions > Negative Emotions for each group at each time point. The scatter plot shows the correlation between the change in neural activity (Post activity minus Pre activity) with the change in behavioral performance (Post score minus Pre score) on the MSCEIT Perceiving Emotions score.

gender may influence the degree or rate of improvement from emotion recognition training. Third, objects were used as the baseline instead of face-processing conditions. Thus, the neural effects of AT + SCT might reflect enhanced processing of both non-emotional and emotional face characteristics. Fourth, social cognition training was only 5–15 min per day. While this suggests that a relatively small amount of social cognition training yields benefits, more intense training may produce larger effects and reveal neural changes in emotion-processing regions, such

as the amygdala, not found here. Finally, participants were paid for their participation which could have influenced motivation and improvement (Brefczynski-Lewis et al., 2007), an important consideration for the translation of cognitive training to clinical practice.

Despite these limitations, the collective data indicate that well-designed behavioral interventions can improve neural function and associated neurocognitive skills in schizophrenia. If confirmed, the potential therapeutic ramifications of this learning-induced neuroplasticity

Table 4
Regions that show a Group (AT + TCT/CG) * Time (Pre/Post) interaction effect in the opposite direction as expected [i.e. AT + SCT had a decrease in activity and/or CG showed an increase in activity from pre to post training].

Anatomical region	R/L	BA	Volume in voxels (mm)	MNI x, y, z coordinates	T value
Negative emotions vs. objects					
Gyrus rectus	L	11	76 (608)	-8 28 -14	5.15
Superior frontal gyrus/Anterior cingulate gyrus	L	32	20 (160)	-8 40 26	4.15
Positive emotions vs. objects					
No significant findings					

Table 5
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 participants n = 22	AT + SCT n = 11	CG n = 11
A. Neural activity change for negative emotions correlated with change in MSCEIT Perceiving Emotions score			
Right postcentral gyrus	.47*	.30	.41
B. Neural activity change for positive emotions correlated with change in MSCEIT Perceiving Emotions score			
Right postcentral gyrus	.60*	.35	.61*
Left angular gyrus	.46*	.60*	-.37
Right superior temporal gyrus/Heschl's gyrus	.29	.08	.06
C. Neural activity change for positive emotions-negative emotions correlated with change in MSCEIT Perceiving Emotions score			
Left precentral gyrus/inferior frontal gyrus [^]	.56*	.26	.42
Left precentral gyrus	.26	-.07	-.20
Right globus pallidus	.19	-.14	-.15
Right superior frontal gyrus	.38	.08	.26

* Correlation is significant at $p < .05$ (two-tailed test).

[^] Results illustrated in Fig. 3.

are far-reaching, for it suggests that individuals with schizophrenia can regain critical neurocognitive skills that are crucial for functional recovery.

Role of funding source

The funding agencies provided funding for the study, but played no other role.

Contributors

Christine Hooker designed the emotion recognition experiment, collected and analyzed the fMRI data, wrote the manuscript, and assisted writing the intervention protocol. Sophia Vinogradov designed the intervention protocols and supervised all aspects of pre/post clinical assessments and participant training. Lori Bruce helped analyze the fMRI data. Melissa Fisher conducted, supervised, and analyzed data from pre/post clinical assessments. Sara Verosky helped collect fMRI data. Asako Miyakawa helped create the fMRI experiment and collect fMRI data.

Conflict of interest

Sophia Vinogradov and Christine Hooker are paid consultants on an NIMH BRDG-SPAN grant to Brain Plasticity Inc. Lori Bruce, Melissa Fisher, Sara Verosky, and Asako Miyakawa report no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2012.05.009>.

References

- Adolphs, R., Damasio, H., Tranel, D., Cooper, G., Damasio, A.R., 2000. A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. *J. Neurosci.* 20 (7), 2683–2690.
- Adolphs, R., Tranel, D., Damasio, A.R., 2003. Dissociable neural systems for recognizing emotions. *Brain Cogn.* 52 (1), 61–69.
- Aleman, A., Kahn, R.S., 2005. Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? *Prog. Neurobiol.* 77 (5), 283–298.
- Barch, D.M., 2005. The cognitive neuroscience of schizophrenia. *Annu. Rev. Clin. Psychol.* 1, 321–353.
- Baron-Cohen, S., Hill, J., Wheelwright, S., 2003. *Mind Reading: the interactive guide to emotions*. Jessica Kingsley Publishers Ltd., University of Cambridge, UK.
- Bilker, W.B., Brensinger, C., Kurtz, M.M., Kohler, C., Gur, R.C., Siegel, S.J., Gur, R.E., 2003. Development of an abbreviated schizophrenia quality of life scale using a new method. *Neuropsychopharmacology* 28 (4), 773–777.
- Brefczynski-Lewis, J.A., Lutz, A., Schaefer, H.S., Levinson, D.B., Davidson, R.J., 2007. Neural correlates of attentional expertise in long-term meditation practitioners. *Proc. Natl. Acad. Sci. U. S. A.* 104 (27), 11483–11488.
- Cohen, A.S., Minor, K.S., 2010. Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies. *Schizophr. Bull.* 36 (1), 143–150.
- Cohen, A.S., Najolia, G.M., Brown, L.A., Minor, K.S., 2011. The state-trait disjunction of anhedonia in schizophrenia: potential affective, cognitive and social-based mechanisms. *Clin. Psychol. Rev.* 31 (3), 440–448.
- Edwards, B.G., Barch, D.M., Braver, T.S., 2010. Improving prefrontal cortex function in schizophrenia through focused training of cognitive control. *Front. Hum. Neurosci.* 4, 32.
- Ekman, P., 2003. *Micro Expressions Training Tool and The Subtle Expressions Training Tool (METT AND SEIT)*. MOZGO Media, Venice, CA.
- Fisher, M., Holland, C., Merzenich, M.M., Vinogradov, S., 2009. Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. *Am. J. Psychiatry* 166 (7), 805–811.
- Green, M.F., 2007. Stimulating the development of drug treatments to improve cognition in schizophrenia. *Annu. Rev. Clin. Psychol.* 3, 159–180.
- Habel, U., Koch, K., Kellermann, T., Reske, M., Frommann, N., Wolwer, W., Zilles, K., Shah, N.J., Schneider, F., 2010. Training of affect recognition in schizophrenia: neurobiological correlates. *Soc. Neurosci.* 5 (1), 92–104.
- Haut, K.M., Lim, K.O., MacDonald III, A., 2010. Prefrontal cortical changes following cognitive training in patients with chronic schizophrenia: effects of practice, generalization, and specificity. *Neuropsychopharmacology* 35 (9), 1850–1859.
- Holt, D.J., Kunkel, L., Weiss, A.P., Goff, D.C., Wright, C.I., Shin, L.M., Rauch, S.L., Hootnick, J., Heckers, S., 2006. Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophr. Res.* 82 (2–3), 153–162.
- Hooker, C., Park, S., 2002. Emotion processing and its relationship to social functioning in schizophrenia patients. *Psychiatry Res.* 112 (1), 41–50.
- Horan, W.P., Blanchard, J.J., Clark, L.A., Green, M.F., 2008. Affective traits in schizophrenia and schizotypy. *Schizophr. Bull.* 34 (5), 856–874.
- Juckel, G., Schlagenhauf, F., Koslowski, M., Wustenberg, T., Villringer, A., Knutson, B., Wrase, J., Heinz, A., 2006. Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage* 29 (2), 409–416.
- Keefe, R.S., Bilder, R.M., Davis, S.M., Harvey, P.D., Palmer, B.W., Gold, J.M., Meltzer, H.Y., Green, M.F., Capuano, G., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Davis, C.E., Hsiao, J.K., Lieberman, J.A., 2007. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Arch. Gen. Psychiatry* 64 (6), 633–647.
- Kurtz, M.M., Richardson, C.L., 2011. Social cognitive training for schizophrenia: a meta-analytic investigation of controlled research. *Schizophr. Bull.* <http://dx.doi.org/10.1093/schbul/sbr036>. (First published online: April 27, 2011).
- Mayer, J.D., Salovey, P., Caruso, D.R., Sitarenios, G., 2003. Measuring emotional intelligence with the MSCEIT V2.0. *Emotion, Washington, D.C* 3 (1), 97–105.
- Namiki, C., Hirao, K., Yamada, M., Hanakawa, T., Fukuyama, H., Hayashi, T., Murai, T., 2007. Impaired facial emotion recognition and reduced amygdalar volume in schizophrenia. *Psychiatry Res.* 156 (1), 23–32.
- Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese III, F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. *Am. J. Psychiatry* 165 (2), 203–213.
- O'Doherty, J., Winston, J., Critchley, H., Perrett, D., Burt, D.M., Dolan, R.J., 2003. Beauty in a smile: the role of medial orbitofrontal cortex in facial attractiveness. *Neuropsychologia* 41 (2), 147–155.
- Ohl, F.W., Scheich, H., 2005. Learning-induced plasticity in animal and human auditory cortex. *Curr. Opin. Neurobiol.* 15 (4), 470–477.
- Pitcher, D., Garrido, L., Walsh, V., Duchaine, B.C., 2008. Transcranial magnetic stimulation disrupts the perception and embodiment of facial expressions. *J. Neurosci.* 28 (36), 8929–8933.
- Polley, D.B., Steinberg, E.E., Merzenich, M.M., 2006. Perceptual learning directs auditory cortical map reorganization through top-down influences. *J. Neurosci.* 26 (18), 4970–4982.
- Sacks, S., Fisher, M., Garrett, C., Alexander, P., Holland, C., Rose, D., Hooker, C.I., Vinogradov, S., in press. Combining computerized social cognitive training with neuroplasticity-based auditory training in schizophrenia. *Clinical Schizophrenia and Related Psychoses*.
- Spreckelmeyer, K.N., Krach, S., Kohls, G., Rademacher, L., Irmak, A., Konrad, K., Kircher, T., Grunder, G., 2009. Anticipation of monetary and social reward differentially activates mesolimbic brain structures in men and women. *Soc. Cogn. Affect. Neurosci.* 4 (2), 158–165.
- Swartz, M.S., Perkins, D.O., Stroup, T.S., Davis, S.M., Capuano, G., Rosenheck, R.A., Reimherr, F., McGee, M.F., Keefe, R.S., McEvoy, J.P., Hsiao, J.K., Lieberman, J.A., 2007. Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. *Am. J. Psychiatry* 164 (3), 428–436.
- Thayer, J.F., Johnsen, B.H., 2000. Sex differences in judgement of facial affect: a multivariate analysis of recognition errors. *Scand. J. Psychol.* 41 (3), 243–246.
- Tsoi, D.T., Lee, K.H., Khokhar, W.A., Mir, N.U., Swalli, J.S., Gee, K.A., Pluck, G., Woodruff, P.W., 2008. Is facial emotion recognition impairment in schizophrenia identical for different emotions? A signal detection analysis. *Schizophr. Res.* 99 (1–3), 263–269.
- Wechsler, D., 1999. *Wechsler Abbreviated Scale of Intelligence*. The Psychological Corporation, San Antonio, TX.
- Wexler, B.E., Anderson, M., Fulbright, R.K., Gore, J.C., 2000. Preliminary evidence of improved verbal working memory performance and normalization of task-related frontal lobe activation in schizophrenia following cognitive exercises. *Am. J. Psychiatry* 157 (10), 1694–1697.
- Wykes, T., Brammer, M., Mellers, J., Bray, P., Reeder, C., Williams, C., Corner, J., 2002. Effects on the brain of a psychological treatment: cognitive remediation therapy: functional magnetic resonance imaging in schizophrenia. *Br. J. Psychiatry* 181, 144–152.
- Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am. J. Psychiatry* 168 (5), 472–485.