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Social impairment in schizophrenia: New approaches for treating a persistent problem

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Abstract

Purpose of Review—Deficits in social cognition are an important determinant of social functioning in schizophrenia, a core feature of the illness that persists despite treatment. Recent research in neuroplasticity-based therapeutics show that neural systems supporting core cognitive skills improve after targeted cognitive training, suggesting that social cognition, and concomitant social functioning, may be improved by targeting the neural systems supporting social cognition. However, the success of this approach depends on the extent to which the social brain is malleable. We review the neural effects of training programs focused on improving social cognition in healthy, schizophrenia, and other clinical samples.

Recent Findings—The current literature suggests that the neural mechanisms underlying social cognition show neuroplastic changes after behavioral training and these neural changes confer concomitant benefits to social cognition and social behavior. Most research in schizophrenia has focused on emotion recognition, and while emotion recognition training has behavioral and neural benefits for schizophrenia, more advanced social cognitive processes need to be examined.

Summary—The data suggest that targeting neural systems underlying social cognition through socially-focused behavioral interventions may improve social functioning impairments in schizophrenia. Questions remain regarding how to optimize training, which should be addressed in future work.

Keywords

social cognition; social functioning; cognitive training; neuroplasticity; schizophrenia

Introduction

The ability to navigate the social environment is a robust predictor of health, well-being, social status, and occupational achievement. The social world –interacting with others, understanding social context, and developing interpersonal relationships– is particularly challenging for people with schizophrenia. These social difficulties do not improve after standard treatments [1,2], and contribute to chronic functional disability [3,*4]. New

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Conflicts of Interest

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treatments for social impairment are necessary, but, thus far, treatment development has been stymied by limited knowledge about the neural systems supporting social behavior.

Here, we review recent advances in social and cognitive neuroscience that support neuroplasticity-based approaches for treating social impairment in schizophrenia. It is well-established that poor social functioning in schizophrenia is caused, in large part, by behavioral deficits in social cognition – a suite of abilities, including emotion recognition, self-regulation, and theory of mind (ToM) (i.e. understanding the mental states of others) [5,6–8]. Recent research demonstrates the following: 1) Social cognitive skills depend on the activity and connectivity of specific brain regions. These include regions primarily involved in *emotion processing* – amygdala, somatosensory-related cortex (SRC), ventral striatum, and medial orbitofrontal cortex (MOFC); *cognitive control (used in self-regulatory processes)* – lateral prefrontal cortex (LPFC), anterior cingulate cortex (ACC), and superior parietal lobe; and *theory of mind* – superior temporal sulcus (STS), temporoparietal junction (TPJ), posterior cingulate, and medial prefrontal cortex (MPFC) [9]; 2) Schizophrenia is associated with neural dysfunction in these regions, and the degree of dysfunction is related to social cognitive performance and real-world social behavior [10,11]; and 3) Cognitive deficits related to neural dysfunction in schizophrenia can be improved through behavioral interventions, such as computer-based cognitive training, that promote neuroplasticity. More specifically, intense behavioral practice of a cognitive skill (e.g., working-memory), improves the underlying neural system supporting that skill, and learning-induced neural changes are related to better cognitive performance [12,13–19]. These data indicate that neuroplasticity-based approaches could improve social impairment in schizophrenia. Theoretically, social cognition training would enhance the function of underlying neural systems, and these neural changes will improve social cognition, which, in turn, will improve social functioning. Moreover, with clearly defined neural targets and reliable neural outcome measures, this proposed mechanism can now be tested.

Below we review: 1) the theory behind neuroplasticity-based approaches, 2) evidence of neuroplasticity in systems supporting social behavior in healthy and clinical populations; and 3) questions to be addressed in future research.

What is a “neuroplasticity-based approach” and how does it differ from other treatments?

Neuroplasticity is an inherent property of the human adult brain that allows for experience-dependent, including learning-induced, changes to neural function [20]. That is, neural function shapes our experience, while, at the same time, our experience shapes neural function. Given that cognition is an emergent property of neural function [12], the dynamic and reciprocal relationship between brain and experience provides an avenue for remediating neural-based deficits in cognition. Neuroplasticity-based treatments capitalize on the brain’s capacity to change by manipulating the content and context of experience to target specific neural systems and shape neural response. For example, cognitive training programs aimed at improving LPFC function in schizophrenia consist of intense behavioral practice of cognitive skills, such as working-memory, that recruit LPFC activity. The repeated engagement of LPFC and associated regions refines LPFC activity and strengthens

functional connectivity with other regions in the working-memory network. Training exercises are designed to enhance the context for learning which optimizes learning-induced neuroplasticity. Learning is enhanced when training is: (a) *intensive and adaptive*: difficulty is kept high such that task demands are always higher than the participant's neurocognitive capacity; (b) *engaging*: requiring directed attention; and (c) *reinforcing*: correct responses are rewarded. These characteristics promote motivation and elicit neuromodulators, such as dopamine and acetylcholine, which enhance the molecular basis of learning (e.g., synaptic plasticity) [21,22]. Cognitive training programs that incorporate these principles produce neural changes that are associated with behavioral improvements in cognition (including social cognition) and day-to-day functioning for healthy individuals [17,18], people with schizophrenia [19,23], and people at risk for schizophrenia [24].

Neuroplasticity-based treatments are distinguished from other treatments by their explicit design to treat problematic behavior by targeting the underlying neural cause and promoting enduring neural changes that will, ultimately, facilitate behavioral improvement. This "brain first" approach is different than behavioral interventions, such as social skills training, which focus on the external behavior. It also differs from other neuroscience-based approaches, such as psychopharmacological interventions, which are not, necessarily, designed to create long-lasting changes to neural structure and function.

Can principles of neuroplasticity be used to improve social impairment?

Evidence of neuroplasticity after targeted cognitive training in schizophrenia suggests that targeted social cognition training may have similar benefits. However, social cognition differs from cognition in a number of ways, and it is unclear how these differences may influence the efficacy of neuroplasticity-based training. The neural systems for social-emotional processing may not be as malleable and/or may not respond to the same training characteristics. While there is indirect evidence that neural systems for social-emotional processing are malleable by social experience, such as long-periods of social deprivation [25–30], the degree of malleability and the characteristics that promote positive neural changes are unknown. Moreover, the social world is highly complex; compared to working memory, social processes may not be as easily isolated and targeted through behavioral training. Social functioning is a reciprocal and context-dependent process in which multiple social and emotional skills influence relationships over time. These dynamic elements of social interactions may not translate easily to training programs and social dilemmas rarely have a single "correct" answer. Furthermore, the notion that social cognition and behavior could be improved through non-social means (e.g., computer-based training that does not involve human-to-human interaction) seems counterintuitive. Yet, the ability to manipulate content, dose, and intensity of social input via computer-based programs could be an efficient avenue for strengthening the targeted neural circuits. Theoretically, strengthening the neural circuits for social processing should enhance the real-world experience of social encounters which would then boost motivation to have additional social experiences, creating a positive, self-sustaining interplay between brain function and behavioral experience.

Emotion Recognition

Social cognition training in schizophrenia has largely focused on emotion recognition and basic ToM skills that involve identifying the mental states of others from observable cues. These social cognitive processes are ideal testing grounds for neuroplasticity-based interventions targeting social behavior. Emotion recognition relies on a well-defined neural network, including the amygdala, superior temporal sulcus (STS), and somatosensory-related cortex (SRC). Emotion recognition skills and associated neural mechanisms are disrupted in schizophrenia-spectrum populations and strongly related to functional outcome [31,32]. Both neural and behavioral performance can be reliably measured, and the computer-based behavioral measures are easily converted into training exercises with characteristics that promote neuroplasticity.

Hooker et al. [33,34] investigated the neural effects of 50 hours of auditory-based cognitive training plus social cognition training consisting of emotion recognition and basic ToM in individuals with schizophrenia. On a facial emotion recognition task, fMRI results demonstrated that, compared to the control intervention of placebo computer games, cognitive plus social cognitive training was associated with neural activity increases in the amygdala and SRC - key regions of the emotion recognition network. Importantly, training-related increases in these regions predicted improvement on a standardized behavioral test of emotion processing. Programs that just include computerized facial emotion training are also associated with neural changes in fMRI [35] and electrophysiological measures, including ERP changes in a parietal-temporal-occipital network implicated in face processing [36], and MEG-related increases in alpha power, which is related to facial emotion recognition [37].

Eack et al. [38] evaluated gray matter volume (GMV) changes in patients who underwent either two years of Cognitive Enhancement Therapy (CET), a treatment that combines group-based social skills training with computer-based cognitive exercises, or Enriched Supportive Therapy (EST). Compared to EST, CET participants demonstrated greater GMV preservation in the hippocampus, parahippocampal gyrus, and fusiform gyrus, and increased GMV in the amygdala – regions that support emotion processing, ToM, memory, and prospection. Moreover, CET-related GMV effects related to performance gains on behavioral tests of social cognition.

To date, only one social cognitive training study has evaluated the association between training-related neural changes and social functioning changes. Subramaniam et al. [39] investigated the effects of 50 hours of computer-based cognitive training combined with training in facial affect recognition and basic ToM (similar to [33,34]) on source monitoring (i.e., distinguishing the source of experiences as being internal versus external); a process that recruits structures involved in self-referential processing and ToM, namely MPFC. Compared to placebo computer games, schizophrenia patients who received active training demonstrated pre-to-post training normalization of MPFC activation, and MPFC activity post-training was associated with better social functioning 6-months later.

In summary, neural networks supporting different aspects of social cognition appear malleable in response to emotion recognition and basic ToM training in schizophrenia. These neural changes are associated with performance gains on social cognitive tasks, and preliminary evidence suggests training-related changes can confer benefits to social functioning.

Self-Regulation/Cognitive Control of Emotion

The regulation of emotional experience/expression and the ability to control the influence of emotion on behavior, termed cognitive control of emotion [40], is a core component of self-regulation necessary for navigating social interactions, particularly interpersonal conflicts [41,42]. Cognitive control of emotion comprises a continuum of processes, ranging from controlling attention to and changing the meaning of perceived/experienced emotions, in which cognitive control circuitry modulates emotion processing regions to control the impact of emotion on experience and behavior [40]. Mounting evidence indicates impaired cognitive control of emotion may be characteristic of the schizophrenia-spectrum [43], arises from dysfunctional activation in cognitive control regions, particularly LPFC [43], and contributes to symptom exacerbation and maladaptive response to social stressors [44,45]. Consequently, interventions that are designed to improve cognitive control of emotion could improve social functioning.

Training studies have predominantly focused on the neural effects of training the explicit and volitional (i.e. effortful) *down*-regulation of negative/undesirable emotions and the implicit attentional control away from negative stimuli. For example, Cognitive Behavioral Therapy (CBT) trains explicit and volitional emotion regulation by emphasizing high-level cognitive strategies, such as problem-solving and reappraisal. CBT is associated with reduced symptoms [46–49] and normalization of LPFC-limbic activation in schizophrenia [50,51], and increased dorsal MPFC with accompanying behavioral gains during reappraisal in social anxiety disorder (SAD) [52]. Thus, explicit training of volitional emotion regulation via CBT effects change in the targeted neural circuitry.

Similarly, Mindfulness, the active, non-judgmental orientation and maintenance of attention to one's current psychophysiological state [53], has been shown to improve well-being, emotional reactivity, and behavioral regulation in multiple clinical populations [54]. In schizophrenia, preliminary behavioral evidence indicates that 12 weekly 90-minute group sessions combining CBT skills training and 10-minutes of mindfulness meditation practice leads to significant pre-to-post improvements in symptoms, well-being, and daily functioning [55].

Neuroimaging studies indicate that Mindfulness Based Stress Reduction (MBSR), a program comprising eight weekly 2.5-hour group classes in meditation (i.e., breath focus, body scan, open monitoring) and a 1-day meditation retreat, is a particularly promising approach. In SAD individuals, participation in MBSR showed pre-to-post training neural activation changes in cognitive control of emotion circuitry and concomitant improvements in explicit emotion regulation using reappraisal [56]. Similarly, an RCT comparing MBSR to Aerobic Exercise in SAD, MBSR training produced increased activation in LPFC and parietal

regions, and decreases in amygdala during reappraisal [57]. These training related changes may be specific to MBSR's mindful meditation component, which likely promotes flexible attentional engagement to negative emotional information and improves volitional attention regulation [58], processes known to be impaired in schizophrenia and associated with social impairment [44]. However, to date, no neuroimaging investigations of mindfulness have been conducted in schizophrenia-spectrum samples.

Training in automatic inhibitory control of emotion may transfer gains to volitional emotion regulation strategies. Twenty days of working memory training on an N-back task utilizing emotional faces as target stimuli resulted in increased efficiency in cognitive control circuitry in healthy individuals [59]. Participants who received training showed reduced LPFC activation during medium cognitive load trials, but increased LPFC activation and accompanying behavioral performance gains on high cognitive load trials. Notably, participants in the training group also demonstrated increased recruitment of attention and cognitive control related regions when regulating emotional response through reappraisal, indicating that training gains can transfer across emotion regulation processes.

Attentional Bias Modification (ABM) targets the attentional control processes involved in emotion perception and experience. ABM use computerized training paradigms to alter attention to emotional stimuli, most commonly using a dot-probe task designed to train attention away from threat-related information (e.g. angry faces). Behavioral studies show ABM results in improved attentional control and accompanying symptom reductions in anxiety, depression, and substance use disorders [60]. Preliminary evidence suggests this effect is mediated by alteration of prefrontal systems involved in the inhibitory control of attention to emotional information. Using fMRI in a sample of healthy individuals, Browning et al. [61] demonstrated altered activation in dorsal and ventral LPFC and changes in connectivity between LPFC and face-sensitive sensory cortex following a single ABM training session. ERP evidence is consistent with this [62]. However, the longevity of ABM-induced neural changes and their effect on social functioning remains unknown, and no studies have examined the use of ABM in schizophrenia.

In summary, evidence suggests that training volitional emotion regulation and automatic inhibitory control of emotional information results in changes to cognitive control of emotion circuitry and that these changes may confer benefits to well-being. However, research examining the trainability of emotion regulation in schizophrenia, and the potential benefits to social functioning, needs further investigation.

Theory of Mind and Prosocial Behavior

To improve social functioning in schizophrenia, social cognitive skills, such as emotion regulation and theory of mind, must be used to in the service of prosocial behavior. For example, emotion regulation could impact social functioning in schizophrenia via deficits in the *up*-regulation of emotions and prosocial feelings, which could contribute to the social anhedonia [45] and reduced reward-related motivation [63] observed in schizophrenia. One such prosocial feeling is compassion, the understanding of another's difficult situation (reliant on ToM) along with the expression of concern and desire to relieve their distress

[64]. The goal of compassion training is to extend feelings of prosocial concern and warmth towards others through meditative/mindfulness practice. Compassion training often involves a theoretical introduction to mindfulness and compassion and skill teaching by a trained instructor, followed by guided practice. During practice, participants perform a mindfulness exercise to orient themselves to the present moment, contemplate someone who they already feel compassion for, and then practice extending those sentiments to others.

Neuroimaging studies in healthy individuals indicate that compassion training leads to changes in neural circuitry supporting ToM, positive emotion, and affiliation. Compared to memory training, compassion training produced activity increases in MOFC, ventral striatum, and ventral tegmentum, while watching videos depicting others in distress [65]. Interestingly, compared to memory training, empathy training (focusing on another's distress) led to increased negative affect and activation in the pain network [66], consistent with data indicating empathy can be emotionally costly [67]. Subsequent compassion training reversed this increase in negative affect, increased positive affect, and led to increased activity in ventral striatum, pregenual anterior cingulate, and MOFC.

Compared to cognitive reappraisal training, compassion training produced increased prosocial behavior on an economic decision-making task accompanied by altered activation in inferior parietal cortex, dorsal LPFC (DLPFC), and DLPFC functional connectivity with ventral striatum (nucleus accumbens, specifically) [68]. Thus, compassion training may promote prosocial behavior via increased engagement in cognitive control-related prefrontal neural circuitry and its connectivity to emotion processing and reward-related regions.

Compassion training also confers beneficial changes to the neural circuitry involved in ToM. Lutz et al. [69] found that compared to non-expert compassion meditators, expert compassion meditators showed increased neural activity in posterior cingulate cortex and right posterior STS/TPJ when listening to sounds of distress. Mascaro et al. [70] found that compassion training versus a health discussion class led to increased activity in left inferior frontal gyrus, DMPFC, and left STS during a mental state decoding task. Neural changes were related to task performance.

Thus, compassion training appears to modulate several networks including those involved in positive affect, ToM, and prosocial behavior. Given the importance of these networks for effective social functioning, compassion training may ameliorate social impairments in schizophrenia. Preliminary behavioral investigations in schizophrenia have shown beneficial effects of compassion training on symptoms and well-being [71–73], but training-related neural effects and putative social functioning improvements have not been investigated.

Conclusion

The studies reviewed here suggest that the social brain is malleable in response to social cognition training and that training-related changes in neural systems underlying social cognition are related to improvement in social cognition performance. Given the strong association between social cognition and social functioning, the reviewed training programs and their variants represent fruitful avenues for improving social impairment in

schizophrenia. Notably, the evidence indicates that social cognition can, in some cases, be improved through non-social methods such as computer-based training. The advantages of computer-based training programs are substantial; given that they more directly target pathophysiological processes, can be delivered through the internet, completed independent of a clinic setting, and may be less stigmatizing.

There is still much work to be done. Many of the training methods reviewed here have not been tested with schizophrenia-spectrum samples. In addition, some training programs, such as compassion training, were not designed to promote neuroplasticity. With regard to these and other social skills interventions, a key question is how to maximize changes to the neural systems of social behavior that will be enduring and self-sustaining. It is also unknown how altering the modality (e.g., computerized games versus in-person groups), intensity, and length of treatment, specific target of treatment (e.g., emotion processing versus ToM), and how person-specific factors such as premorbid functioning, motivation, and expectations, affect neural outcomes.

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Key Points

- Improving the neural mechanisms underlying social cognition through neuroplasticity-based targeted cognitive training may confer benefits to social cognitive ability and real world social functioning.
- Recent work in cognitive control of emotion training, compassion training, and social cognitive skills training support the idea that the neural mechanisms underlying these processes are malleable and, in some cases, confer benefits to cognition and behavior.
- Future work should evaluate how to optimize neuroplasticity-based training in social cognition.