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REVIEW

Neuroplastic Changes Following Social Cognition Training in Schizophrenia: A Systematic Review

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Abstract Social cognitive impairment is a key feature of schizophrenia and social cognition training (SCT) is a promising tool to address these deficits. Neurobiological dysfunction in schizophrenia has been widely researched, but neuronal changes induced by SCT have been scarcely explored. This review aims to assess the neuroplastic effects of SCT in patients with schizophrenia spectrum disorders. PubMed and Web of Science databases were searched for clinical trials testing the effects of SCT in functional and structural brain measurements of adult patients with schizophrenia or schizoaffective disorders. A total of 11 studies were included: five used fMRI, two used EEG and ERP, one used ERP only, two used MEG and one study used MRI. Data extracting and processing regarding sociodemographic and clinical variables, intervention characteristics, neuroimaging procedures, neuroplastic findings, effect sizes and study quality criteria was completed by two raters. Results indicate a wide range of structural and functional changes in numerous regions and circuits of the social brain, including early perceptual areas, the limbic system and prefrontal regions. Despite the small number of trials currently available, evidence suggests that SCT is associated with neuroplastic changes in the social brain and concomitant improvements in social cognitive performance. There is a lack of extensive knowledge about the neural mechanisms that underlie social cognitive enhancement after treatment, but the reported findings may shed light on the neural substrates of social cognitive impairment in schizophrenia and how improved treatment procedures can be developed and applied.

Keywords Schizophrenia · Social cognition · Social cognition training · Neuroimaging · Neuroplasticity

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Introduction

Social cognition impairment is considered a key feature of schizophrenia and an important predictor of functional outcomes (Fett et al. 2011; Kern et al. 2009; Kurtz and Richardson 2012; Savla et al. 2013; Wölwer and Frommann 2011). Patients with schizophrenia display impairments in several social cognitive domains, including facial emotion recognition (FER), theory of mind (ToM), social perception and attributional styles (Farkas and Anthony 2010; Kern et al. 2009; Kurtz and Richardson 2012; Savla et al. 2013; Wölwer and Frommann 2011). These deficits are generally present

before the onset of the first psychotic episode and tend to be persistent and stable over the course of illness (Kurtz and Richardson 2012; Robertson et al. 2014).

Social cognition includes several complex cognitive processes that allow people to understand and gather information about the self, other persons and interpersonal norms of the surrounding social world. Modern brain imaging techniques have allowed researchers to identify several interconnected brain regions that reliably activate during social cognitive probe tasks. These regions demonstrate an intricate interaction between cortical and subcortical structures, but they also maintain some degree of specialization (Dima et al. 2011; Pessoa and Adolphs 2010; Keysers and Gazzola 2006; Burns 2006, 2004).

Several authors have postulated that social cognitive processes are mainly controlled by cortical midline structures, particularly the prefrontal cortex (PFC; Forbes and Grafman 2010; Bicks et al. 2015). The medial PFC has been linked to high-level mental processes which require conscious attribution and judgment of mental states, intentions or even enduring traits of one's self and others (Amodio and Frith 2006). Furthermore, the ventrolateral PFC has been primarily associated with contextual or social appropriateness of responses to social cues (Spreng et al. 2009).

On the other hand, transitory social inferences regarding others' intentions or goals are more perceptual in nature, rely directly on observed behaviors, and are mainly processed within the temporoparietal junction, the superior temporal sulcus and the occipitotemporal regions (Siegal and Varley 2002; Adolphs 2003; Uddin et al. 2007; Keysers and Gazzola 2007; Saxe and Powell 2006). ToM tasks have been systematically associated with the temporoparietal junction (Saxe and Kanwisher 2003; Saxe and Powell 2006), while the posterior regions of the superior temporal sulcus have been linked to the processing of changeable features of human faces, allowing subjects to infer others' affective and intentional states (Ishai et al. 2005).

Primary sensory cortices and limbic structures such as the amygdala also play a critical role in social cognition as they provide sensory information to other cortical regions responsible for analyzing particular aspects or categories of stimulus (e.g. bodies or faces; Adolphs 2009). It has been suggested that the amygdala plays a critical role in emotion processing as it mediates the biological salience associated with external stimuli such as facial expressions (Santos et al. 2011).

In recent years, researchers have recognized the importance of social cognitive dysfunction and its underlying neurobiological mechanisms in schizophrenia patients (Thorsen et al. 2014). As such, the development of treatment methods to effectively remedy social cognitive deficits has become a major focus of researchers and clinicians (Green et al. 2004; Hooker et al. 2012; Kurtz and Richardson 2012).

Several studies have suggested that pharmacological intervention is an ineffective tool in the treatment of these impairments (Hooker et al. 2012; Kucharska-Pietura and Mortimer 2013; Kurtz and Richardson 2012). Conversely, social cognition training (SCT) has shown great promise in the improvement of social cognition and functioning (Farkas and Anthony 2010; Kern et al. 2009; Kurtz et al. 2016). A recent meta-analysis of SCT for patients with schizophrenia found moderate to large effect sizes in the improvement of emotion recognition and small to moderate effects on ToM, as well as moderate to large effects on measures of community functioning and overall symptoms in comparison to control groups (Kurtz and Richardson 2012).

SCT is delivered through a variety of programs that can be divided into broad-based, comprehensive and targeted approaches. Broad-based programs such as Integrated Psychological Therapy and Cognitive Enhancement Therapy include social cognitive elements within the context of other psychosocial interventions. Integrated Psychological Therapy combines cognitive remediation with psychosocial rehabilitation techniques and has demonstrated effectiveness in improving psychosocial functioning and social cognition (Roder et al. 2006, 2011). Alternatively, Cognitive Enhancement Therapy uses comprehensive SCT together with cognitive remediation and has demonstrated significant improvements on social cognitive measures (Hogarty et al. 2004).

In comparison, comprehensive approaches address several social cognitive impairments in the absence of other psychosocial treatments; the most common programs are Social Cognition and Interaction Training (SCIT; Penn et al. 2007; Combs et al. 2007; Roberts et al. 2010; Roberts and Penn 2009) and Social Cognitive Skills Training (SCST; Horan et al. 2011; Horan et al. 2009). SCIT focuses on emotion perception, ToM, and attributional biases, and has demonstrated improvements in all of these domains. SCST focuses on emotion processing, social perception, attributional biases, and ToM, and has demonstrated improvements in FER and emotion management. Finally, there are targeted interventions that focus on single social cognitive domains. One such intervention is Training of Affect Recognition, which has been shown to effectively improve emotion recognition (Wölwer et al. 2005; Frommann et al. 2003). Another example is Emotion and ToM Imitation Training, which has also demonstrated improvements in social cognitive processes including empathy and ToM (Mazza et al. 2010).

The underlying theoretical framework for SCT is based on cognitive neuroscience, which assumes that at any stage throughout life the brain is able to restore itself using neuroplastic and neurogenesis mechanisms (Barlati et al. 2013; Dodell-Feder et al. 2015; Saperstein and Kurtz 2013; Savla et al. 2013; Wykes et al. 2011). Modern neuroscience suggests that neurogenesis occurs more often than previously thought. As such, repeated learning experiences within the stimulating environment provided by SCT may encourage changes in brain activity, resulting in improved social cognition. These mechanisms presumably rely on the brains' plastic

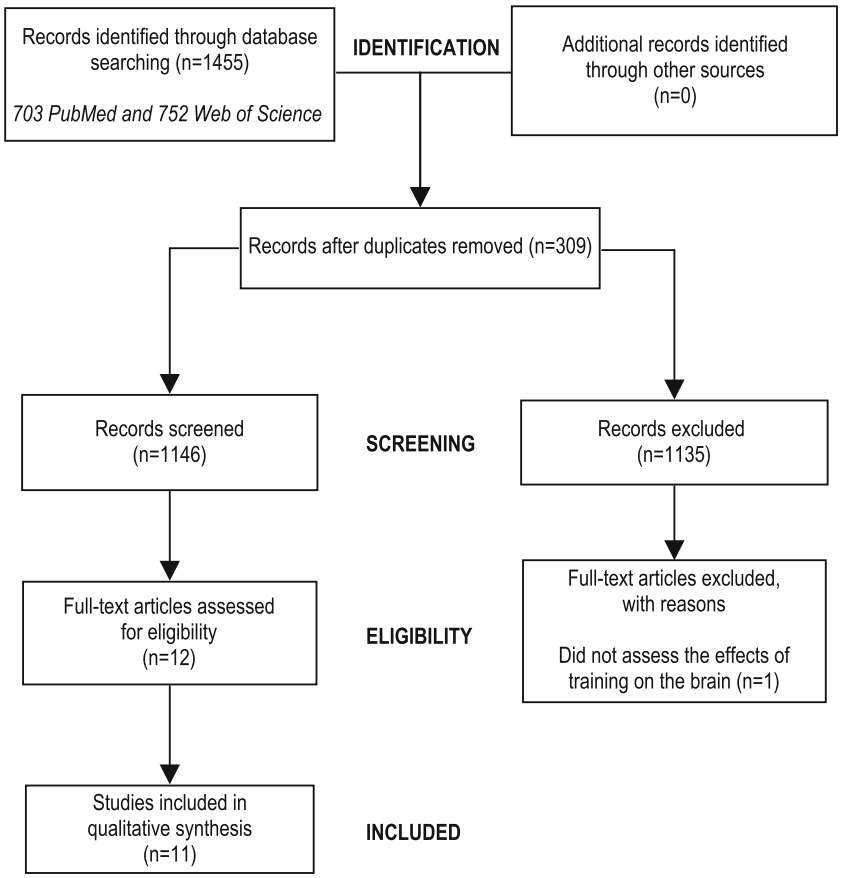

Fig. 1 Study selection process (Moher et al. 2009)

abilities in order to augment neural changes that might allow for better cognitive and social functioning (Barlati et al. 2013). As reported by Kurtz and Richardson (2012), SCT can improve social cognitive outcomes and it might be expected that these changes are thus accompanied by specific neuroplastic changes. Currently, the literature postulates that SCT causes neuroplastic changes in the social brain and that these changes are associated with improvements in social cognition and social behavior (Dodell-Feder et al. 2015). Using functional and structural brain measurement methods in SCT trials will allow researchers to investigate the association between improvements in social cognition and structural changes in the brain. Recently there has been an increasing number of trials using neuroimaging methods to assess SCT efficacy. Identifying key brain regions might help future researchers identify which brain regions to assess in outcome studies and might even aid in identifying new targets for pharmacological interventions. It is clearly necessary to systematically review the existing literature in order to synthesize current findings and guide future research. The aim of this review is to systematically analyze clinical trials addressing the neuroplastic effects of SCT in patients with schizophrenia spectrum disorders through the use of functional and structural brain measurements.

Methods

Relevant studies were systematically searched on PubMeb and Web of Science (Web of Science Core Collection) databases through July 31, 2015. Included trials and important reviews regarding SCT and cognitive remediation were also manually screened for additional relevant studies. This systematic review was conducted taking into consideration the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009).

Eligibility Criteria

The eligibility criteria for study inclusion were developed according to the PICOS strategy, and were as follows: (1) participants in the SCT groups must have diagnoses of schizophrenia or schizoaffective disorder; (2) the intervention must be a SCT program, defined as any kind of intervention using social cognitive stimuli, providing clients with training exercises designed to improve on one or more areas of social cognition; (3) SCT must be compared to active or waiting control groups (CG) or treatment-as-usual (TAU); (4) outcomes must include functional or structural brain measurement to examine potential neuroplastic changes; (5) any kind

of experimental design was acceptable, regardless of randomization procedures or type of control condition; (6) the study must be published in the English language between 2000 and 2015; (7) all participants must be at least 18 years old.

Search and Selection Strategy

Search terms were defined based on population (schizophrenia), intervention (SCT terminology) and assessment procedures (neuroimaging methods). Keywords selected were "schizophrenia" OR "psychosis" AND "social cognitive" OR "emotion recognition" OR "affect recognition" OR "theory of mind" OR "cognitive" AND "training" OR "rehabilitation" OR "therapy" OR "intervention" OR "treatment" AND "functional magnetic resonance imaging" OR "fMRI" OR "magnetic resonance imaging" OR "MRI" OR "positron emission tomography" OR "PET" OR "electroencephalography" OR "EEG" OR "event-related potentials" OR "ERP" OR "diffusion tensor imaging" OR "DTI" OR "near-infrared spectroscopy" OR "NIRS" OR "magnetoencephalography" OR "MEG".

After the initial database search, results were reviewed in order to identity duplicate entries. Next, each title and abstract were screened and excluded if they did not meet eligibility criteria. Finally, the full text of the remaining studies was reviewed, and consensus meetings between two authors (C.C. and S.S.) were held when required for a specific manuscript.

Extraction and Processing Data

Data collected from the studies included general characteristics (title, authors and publication date), methodology, and the most relevant results and conclusions. Regarding methodology, the following information was collected: study design; functional and structural brain measurements; experimental tasks; sample size; type of population (e.g. inpatients or outpatients); identification and description of the interventions; identification method of participants included for imaging analysis; standardized assessment measures; sociodemographic information (means and standard deviations of age and years of education; relative frequencies of gender); clinical data (means and standard deviation of IQ, symptom severity, duration of illness, and chlorpromazine equivalent medication dosages); and methodological quality ratings.

Main effects of treatment were also computed using the Cohen's *d* statistic of effect size. This calculation was only completed for significant findings regarding brain areas or electrophysiologic indicators relevant for social cognitive functioning. Cohen's *d* was calculated as the difference in change scores between intervention type (i.e., treatment versus CG), or the within group change in the treatment group, expressed in standard deviation units (Mpost exp.-Mpost control/SDpooled across groups). By expressing the effect size in standard deviation units, it is possible to make a direct comparison of outcomes across studies. Effect sizes were computed using an online calculator (http://www.psychometrica.de/effect_size.html) developed by Lenhard and Lenhard (2016). Effect sizes were classified according to Lipsey and Wilson (2001) as small ($d < 0.2$), small to moderate ($d = 0.2$–0.4), moderate to large ($d = 0.5$–0.8) and large ($d > 0.8$). When the original papers did not provide sufficient data to compute the effect size, supplemental materials were consulted and the authors were contacted in order to provide the required data. Only one author sent the required information, and as such it was not possible to calculate effect sizes for 5 of the included studies.

Each of the previously mentioned components was collected in a standardized manner by two researchers (C.C. and S.S.) and a consensus meeting was held to review the data collected. In addition, a summary of sample characteristics of the eleven studies included in the analysis was created based on the weighted means of the sociodemographic and clinical characteristics. When studies totally or partially shared the same sample, only the most recent study was included to compute weighted means. Symptom severity was computed based on Positive and Negative Syndrome Scale score (PANSS; Kay et al. 1987).

Finally, we assessed each study according to a 5-point quality rating scale adapted from the work of Kurtz et al. (2016) using the following criteria: 1 point for the use of randomization procedures, 1 point for description of fidelity maintenance, 1 point for blindness of raters, 1 point for gold standard diagnostic criteria, and 1 point for active control condition in the study design. All studies characteristics were coded independently by two raters (S.S and C.C.) in 100 % of the studies to ensure reliability of extraction of study characteristics. No discrepancies were found between the two raters.

Results

A total of 1455 records were identified (703 on PubMed and 752 on Web of Science), from which 309 duplicate citations were removed, leaving 1146 records. Titles and abstracts were screened and 1134 records were excluded because they did not meet the defined eligibility criteria. The full texts of the remaining 12 reports were reviewed and one was excluded because it did not assess the effects of SCT on measures of brain neuroplasticity. As such, 11 studies met our eligibility criteria and were included in the review (Fig. 1).

Sociodemographic and clinical characteristics of the participants in the included studies are described in Tables 1 and 2. Most participants were diagnosed with schizophrenia, although four of the studies also included individuals with schizoaffective disorder (Eack et al. 2010; Keshavan et al.

Table 1 Included studies description: Sociodemographic and clinical information of participants

Study Authors	Sample Size	Population	In/ Outpatient	Age (Mean and SD)	Gender (% Male)	Years of Education (Mean and SD)	IQ (Mean and SD)	Symptom Severity (Mean and SD)	Duration of Illness (Years - Mean and SD)	CPZ (Mean and SD)
Eack et al. (2010)	CET = 30 EST = 23	Schizophrenia or schizoaffective disorder	Outpatients	CET = 25.99 (6.54) EST = 26.42 (6.60)	CET = 63 % EST = 70 %	Attended College CET = 73 % EST = 74 %	CET = 97.90 (7.74) EST = 98.83 (10.24)	*BPRS* CET = 39.47 (9.21) EST = 40.09 (11.03)	CET = 3.17 (2.32) EST = 3.28 (2.08)	CET = 412.2 (343.58) EST = 417.6 (309.85)
Habel et al. (2010b)	TAR = 10 TAU = 10 HC = 10	Schizophrenia	Inpatients or outpatients	TAR = 31.4 (7.8) TAU = 33.7 (10.65) HC = 31.6 (8.8)	TAR = 100 % TAU = 100 % HC = 100 %	TAR = 10.9 (4.0) TAU = 9.1 (2.3) HC = 8.8 (2.0)	TAR = 113.6 (18.6) TAU = 109.2 (14.91)	*PANSS* TAR = 68 TAU = 57.5	Not reported	Not reported
Hooker et al. (2012)*	AT + SCT = 11 CG = 11	Schizophrenia or schizoaffective disorder	Outpatients	AT + SCT = 51.2 (5.8) CG = 41.0 (8.4)	AT + SCT = 90.9 % CG = 72.7 %	AT + SCT = 13.7 (2.2) CG = 12.8 (2.5)	AT + SCT = 98.2 (18.7) CG = 103.6 (19.4)	*PANSS* AT + SCT = 76.2 (15.4) CG = 68.1 (16.3)	AT + SCT = 28.0 (8.3) CG = 20.6 (11.6)	AT + SCT = 252.5 (339) CG = 371.4 (456)
Hooker et al. (2013)*	AT + SCT = 11 CG = 11	Schizophrenia or schizoaffective disorder	Outpatients	AT + SCT = 51.2 (5.8) CG = 41.0 (8.4)	AT + SCT = 90.9 % CG = 72.7 %	AT + SCT = 13.7 (2.2) CG = 12.8 (2.5)	AT + SCT = 98.2 (18.7) CG = 103.6 (19.4)	*PANSS* AT + SCT = 76.2 (15.4) CG = 68.1 (16.3)	AT + SCT = 28.0 (8.3) CG = 20.6 (11.6)	AT + SCT = 252.5 (339) CG = 371.4 (456)
Luckhaus et al. (2013)	SZ = 18 Brief psychotic episode = 1	Schizophrenia or brief psychotic episode	Not reported	35.3 (8.2)	100 %	Not reported	95.3 (13.9)	*PANSS* 56.7 (14.6)	9.4 (8.8)	858.6 (458.4)
Mazza et al. (2010)	ETIT = 16 PST = 17	Schizophrenia	Outpatients	ETIT = 24.37 (2.12) PST = 24.71 (2.17)	SZ = 57.8 %	ETIT = 12.6 (1.25) PST = 10.3 (2.57)	ETIT = 87.8 (7.9) PST = 87.9 (6.3)	*BPRS* ETIT = 78 (5.2) PST = 84.5 (10.6)	ETIT = 0.52 (0.21) PST = 0.54 (0.33)	654.83 (513.2)
Popov et al. (2015)†	FAT = 19 BFP = 19 TAU = 19 HC = 28	Paranoid–hallucinatory schizophrenia or schizoaffective disorder	Inpatients	FAT = 39.21 (7.91) BFP = 36.95 (8.44) TAU = 35.00 (10.59) HC = 29.32 (9.50)	FAT = 52.63 % BFP = 68.42 % TAU = 78.95 % HC = 50 %	FAT = 14.68 (4.19) BFP = 14.56 (3.29) TAU = 14.42 (2.99) HC = 14.55 (3.44)	FAT = 109.79 (16.13) BFP = 101.47 (13.46) TAU = 108.21 (17.89)	*PANSS* FAT = 71.68 BFP = 69.26 TAU = 67.21	Not reported	FAT = 671 (343) BFP = 544 (490) TAU = 617 (403)
Popova et al. (2014)†	FAT = 19 CE = 19 TAU = 19 HC19 = 19 HC24 = 24	Paranoid-hallucinatory schizophrenia	Inpatients	FAT = 39.6 (7.9) CE = 36.0 (8.5) TAU = 35.9 (10.6) HC19 = 27.0 (3.7) HC24 = 31.8 (5.4)	FAT = 57.9 % CE = 63.2 % TAU = 78.9 % HC19 = 63.2 % HC24 = 41.7 %	FAT = 11.5 (1.7) CE = 10.8 (1.7) TAU = 11.3 (1.8) HC19 = 13.0 HC24 = 12.0	FAT = 108.1 (16.3) CE = 102.3 (13.6) TAU = 108.7 (17.4)	*PANSS* FAT = 72.2 CE = 69 TAU = 69.4	Not reported	FAT = 539.6 (289.2) CE = 506.1 (344.3) TAU = 637.9 (280.9)
Stroth et al. (2015)	SZ = 16 HC = 16	Schizophrenia	Inpatients and outpatients	SZ = 36.69 (11.37) HC = 33.69 (8.82)	SZ = 66.67 % HC = 78.57 %	SZ = 11.69 (1.58) HC = 13.25 (0.78)	SZ = 103.88 (11.97) HC = 119.33 (11.93)	*PANSS* SZ = 50.3	10.67 (8.6)	607 (421)
Subramaniam et al. (2012)‡	SZ-AT = 16 SZ-CG = 15 HC = 16	Schizophrenia	Outpatients	SZ = 40 (11.7) HC = 45 (11.6)	SZ = 83.9 % HC = 68.8 %	SZ = 13 (0.89) HC = 14 (1.35)	SZ = 103 HC = 115	*PANSS* SZ-AT = 77.1 SZ-CG = 74.4	SZ = 19.4	SZ-AT = 478 (380) SZ-CG = 419 (453)

Table 1 (continued)

Study Authors	Sample Size	Population	In/ Outpatient	Age (Mean and SD)	Gender (% Male)	Years of Education (Mean and SD)	IQ (Mean and SD)	Symptom Severity (Mean and SD)	Duration of Illness (Years - Mean and SD)	CPZ (Mean and SD)
Subramaniam et al. (2014)‡	SZ-AT = 16 SZ-CG = 14 HC = 15	Schizophrenia	Not reported	SZ-AT = 40.69 (12.7) SZ-CG = 41.21 (9.48) HC = 44.27 (11.2)	SZ-AT = 75 % SZ-CG = 71.4 % HC = 73.3 %	SZ-AT = 13.19 (2.45) SZ-CG = 13.36 (1.82) HC = 13.93 (1.44)	SZ = 103	*PANSS* SZ-AT = 77.1 SZ-CG = 74.7	SZ = 19.4	SZ-AT = 478 (380) SZ-CG = 410 (445)

*These studies ran in parallel; † The samples from these studies may share some participants; ‡ These studies used the same sample and training procedures, but different experimental tasks

SZ = schizophrenia: CET = Cognitive Enhancement Therapy; EST = Enriched Supportive Therapy; PANSS = Positive and Negative Syndrome Scale; BPRS = Brief Psychiatric Rating Scale; TAR = Training of Affect Recognition; TAU = treatment as usual; HC = healthy controls; AT + SCT = Auditory-based cognitive training plus social cognition training; CG = Computer games control group; ETIT = Emotion and ToM Imitation Training; PST = Problem Solving Training; FAT = Facial Affect Recognition Training; BFP = Brain Fitness Program; CE = cognitive exercises; HC19 = was recruited when SZ were provided a pre−/post-intervention comparison of oscillatory activity in the Facial Affect Recognition outcome criterion task; HC24 = was recruited after the MEG study ended, in order to provide a normative performance standard for the newly developed Facial Affect Training tasks; SZ-AT = active computerized cognitive training; SZ-CG = Schizophrenia computer game control group

2011; Hooker et al. 2012; Hooker et al. 2013; Popov et al. 2015). SCT groups ranged from 10 (Habel et al. 2010b) to 30 (Eack et al. 2010) participants, with an average of 72.86 % of the participants being male and mean ages ranging from 24.37 (Mazza et al. 2010) to 51.2 years (Hooker et al. 2012; Hooker et al. 2013), with an overall average age of 34.31. Most studies reported high education levels within the SCT group, with years of education ranging from 10.9 (Habel et al. 2010b) to 14.68 (Popov et al. 2015), with an overall mean of 12.94 years.

With regard to the clinical characteristics of the SCT group, studies included individuals with early psychosis as well as those with chronic psychotic disorders, with illness duration ranging from 0.52 (Mazza et al. 2010) to 28.0 years (Hooker et al. 2012; Hooker et al. 2013). PANSS total score was fairly consistent across studies, ranging from 50.3 (Stroth et al. 2015) to 78 (Mazza et al. 2010). Regarding pharmacological treatment, only Habel et al. (2010b) did not report chlorpromazine equivalent dose within the SCT group; the reported values ranged from 252.5 (Hooker et al. 2012; Hooker et al. 2013) to 858.6 (Luckhaus et al. 2013) and averaged 567.27 mg/day. None of the studies reported significant changes in medication during the trials. Most participants received second generation antipsychotics, although two studies did not report any information regarding medication type (Hooker et al. 2013; Hooker et al. 2012). Finally, IQ values were abnormally high for a schizophrenia sample (Fioravanti et al. 2005; Hedman et al. 2013; Woodberry et al. 2008), ranging from 87.8 (Mazza et al. 2010) to 113.6 (Habel et al. 2010b), with an average of 100.47.

SCT intervention characteristics from each trial are described in Table 3. Five studies used broad-based approaches, with two studies combining auditory-based cognitive training with SCT, two studies using computerized neurocognitive, FER and ToM exercises, and one utilizing a Cognitive Enhancement Therapy protocol. The remaining six studies used targeted SCT approaches, with three studies using Training Affect Recognition, two studies using Facial Affect Recognition Training and one using Emotion and ToM Imitation Training.

Finally, neuroimaging procedures, methodological features and major neuroplastic findings are presented in Table 4. One study used MRI, five used fMRI, two used EEG and ERP, one used ERP alone, and two used MEG. No studies using PET, NIRS or DTI were identified. None of the studies used the same experimental task, although seven studies used some kind of FER-related task. Paired click, reality monitoring and N-back tasks were also used (one study each). It should also be noted that two of the articles resulted from the same trial, although they report different research goals (Hooker et al. 2013; Hooker et al. 2012). Additionally, the studies from Subramaniam et al. (2014) and Subramaniam et al. (2012) reported findings regarding the same sample of participants and Popov et al. (2015) and Popova et al. (2014) may have shared participants in their samples.

Table 2 Summary of sample characteristics within the SCT groups

	Mean or %	N studies	N participants
Participants	100 %	8	137
Age	34.31	8	137
Gender (% males)	72.86 %	8	137
Education	12.94	6	88
IQ (estimate or full-scale)	100.47	8	137
Duration of illness	9.92	6	108
PANSS Total	65.89	6	91
PANSS Positive	15.37	5	80
PANSS Negative	16.24	5	80
Chlorpromazine equivalent dose (mg/day)	567.27	7	127

When studies totally or partially shared the same sample, only the most recent study was included to compute weighted means; PANSS = Positive and Negative Syndrome Scale

MRI

Only one study used structural MRI techniques to compare a broad-based SCT program to an active CG (Eack et al. 2010). The authors reported statistically significant changes in gray matter volume in several medial temporal areas after the SCT intervention in comparison to the CG, including the left parahippocampal gyrus (d = 0.243), left fusiform gyrus (d = 0.243), left amygdala (d = 0.287) and left hippocampus (d = 0.31). Participants in the SCT group actually displayed increased left amygdala gray matter volume and reduced loss in the left parahippocampal and fusiform gyrus in comparison to the active CG. Also, a smaller volume loss of gray matter in the left parahippocampal and fusiform gyrus, as well as a increase in the volume of the left amygdala, significantly mediated the two-year improvement in social cognition (p = 0.039; p = 0.033; p = 0.029, respectively).

fMRI

Five studies used fMRI as an imaging method. Habel et al. (2010b) utilized the Facial Affect Recognition task by Erwin et al. (1992) as the experimental task to assess the effects of an SCT intervention targeting FER when compared to a TAU group. The authors found significant activation increases in several regions in the SCT group in comparison to TAU patients, including the left superior and middle occipital gyrus, the right superior and inferior parietal, the bilateral inferior frontal gyrus, the middle frontal gyrus and the left cerebellum (slight increase). Improved performance in emotion recognition was positively correlated with regional activations in the right inferior frontal gyrus, the right middle frontal gyrus, the bilateral superior frontal gyrus, the right inferior parietal gyrus, the bilateral middle temporal gyrus, the left inferior temporal gyrus, the bilateral cuneus, the right postcentral gyrus, the cerebellum and the insula. There were not sufficient data to compute effect sizes.

Hooker et al. (2012) and Hooker et al. (2013) also used fMRI to compare the effects of combining SCT and computerized auditory-based cognitive training with an active CG that completed regular computer games, such as visuospatial puzzles, solitaire, and checkers. Hooker et al. (2012) developed an experimental emotion recognition task and found intervention-related activation increases in the right postcentral gyrus for both negative emotion vs object contrast (d = 2.10) and positive emotion vs object contrast (d = 1.89) for the auditory training plus SCT group in comparison to the CG. Significant changes regarding positive emotion vs objects contrast activation were also reported in the right superior temporal gyrus (d = 1.82). Improved performance in emotion recognition from the pooled sample was correlated with changes in right postcentral gyrus activity when recognizing negative (r = 0.47) and positive emotions (r = 0.60). Although there were no significant between-group activation changes in the left angular gyrus or precentral gyrus, improved perceived emotion performance was significantly correlated with activation increases from the pooled sample in the positive emotion vs object contrast (r = 0.46) and positive vs negative emotion contrast (r = 0.56), respectively.

In the other study conducted by Hooker et al. (2013), researchers developed an alternative FER task to assess intervention effects. The authors reported that the auditory training plus SCT group showed significant increased activation in the left and right amygdala (d = 1.90; d = 1.51, respectively) for the accurate recognition of open-face emotions (happiness, surprise and fear) in comparison to CG participants. In the intervention group, improvements in emotion perception were significantly correlated with increase in right amygdala activity (r = 0.84) and trended towards significance in the left amygdala (r = 0.59). Pooled data from all participants demonstrated significant correlations between improvements in

Table 3 Included studies description: Interventions characteristics

Study Authors	Social cognition training intervention	Dose (session length)	Frequency (sessions per week)	Duration	Modality	Setting	Follow up
Eack et al. (2010)	CET	SCT: 90 min CT: 60 min	Weekly	2 years SCT: 45 h CT: 60 h	Computer-assisted neurocognitive training and group-based social-cognitive exercises.	Outpatient research clinic	No follow-up.
Habel et al. (2010b)	TAR	45 min	2 Days / week	6 weeks	Computer based affect recognition training and paper-pencil tasks.	Inpatients or outpatients.	No follow-up.
Hooker et al. (2012) *	AT + SCT	AT: 60 min SCT: 5–15 min	5 Days / week.	10 weeks	Computer based auditory training and social cognition training.	Laboratory setting or at home	No follow-up.
Hooker et al. (2013) *	AT + SCT	AT: 60 min SCT: 5–15 min	5 Days / week	10 weeks	Computer based auditory training and social cognition training.	Laboratory setting or at home	No follow-up.
Luckhaus et al. (2013)	TAR	60 Minutes	2 Days / week	6 weeks	Computer based affect recognition training and paper-pencil tasks.	Not reported	2 Months.
Mazza et al. (2010)	ETIT	50 Minutes	2 Days / week.	12 weeks	Group-based intervention to improve theory of mind and empathy (also uses computer exercises)	Outpatients	No follow-up.
Popov et al. (2015) †	FAT	60 Minutes	5 Days / week.	4 weeks	Computer based facial affect recognition training.	University inpatient unit	No follow-up.
Popova et al. (2014) †	FAT	60 Minutes	5 Days / week.	4 weeks	Computer based facial affect discrimination training.	Inpatients of clinical settings.	No follow-up.
Stroth et al. (2015)	TAR	45–60 Minutes	2 Days / week.	6 weeks	Computer based affect recognition training and paper-pencil tasks.	In and out patients.	No follow-up.
Subramaniam et al. (2012) ‡	Broad-base active computerized training	CT: 60 min CT + SCT: 75 min	5 Days / week.	CT: 10 weeks CT + SCT: 6 weeks	Computer-based auditory/verbal, visual, facial emotion recognition and theory of mind.	Community mental health centers and outpatient clinics.	6 Months.
Subramaniam et al. (2014) ‡	Broad-base active computerized training	CT: 60 min CT + SCT: 75 min	5 Days / week	CT: 10 weeks CT + SCT: 6 weeks	Computer-based auditory/verbal, visual, facial emotion recognition and theory of mind.	Not reported	6 Months.

*These studies ran in parallel; † The samples from these studies may share some participants; ‡ These studies used the same sample and training procedures, but different experimental tasks

CET = Cognitive Enhancement Therapy; SCT: Social Cognition Training; CT: Cognitive Training; TAR = Training of Affect Recognition; AT + SCT = Auditory-based cognitive training plus social cognition training; ETIT = Emotion and ToM Imitation Training; FAT = Facial Affect Recognition Training;

Table 4 Included studies descriptions: methodological features, neuroimaging procedures and neuroplastic findings

Study authors	Treatment condition	Control condition	Study design	Methodological quality ratings (1–5)	Sample included for Analysis	Imaging method	Experimental task	Social Cognition outcome measures	Neuroplastic Findings
Eack et al. (2010)	CET	EST	RCT	Study quality rating of 3: randomization; gold-standard diagnostic criteria; active control.	CET = 23 EST = 19	MRI	N/a	MSCEIT	Reduced gray matter loss or increased volume in several medial temporal areas after CET in comparison to EST: - Hippocampus (d = 0.310) - Parahippocampus (d = 0.243) - Fusiform gyrus (d = 0.247) - Amygdala (d = 0.287)
Habel et al. (2010b)	TAR	TAU	RCT	Study quality rating of 2: randomization; gold-standard diagnostic criteria.	TAR = 10 TAU = 10	fMRI	Facial affect recognition task (Erwin et al. 1992).	Emotion discrimination task	Increased activation in several brain regions after TAR in comparison to TAU: - Left superior and middle occipital gyrus - Right superior and inferior parietal cortex - Left inferior frontal operculum - Right Inferior frontal gyrus - Left middle frontal gyrus - Left cerebellum
Hooker et al. (2012) *	AT + SCT	CG	RCT	Study quality rating of 5: randomization; fidelity maintenance; blinded raters; gold-standard diagnostic criteria; active control.	AT + SCT = 11 CG = 11	fMRI	Emotion recognition task (as described by the authors)	MSCEIT	Increased activation in several brain regions after AT + SCT in comparison to CG: - Right postcentral gyrus (Negative vs Objects contrast; d = 2.10) - Right postcentral gyrus (Positive vs Objects contrast; d = 1.89) - Right superior temporal gyrus (Positive vs Objects contrast; d = 1.82)
Hooker et al. (2013) *	AT + SCT	CG	RCT	Study quality rating of 5: randomization; fidelity maintenance; blinded raters; gold-standard diagnostic criteria; active control.	AT + SCT = 11 CG = 11	fMRI	Facial emotion recognition task (Ekman and Matsumoto 1993; Gur et al. 2002; Goeleven et al. 2008).	MSCEIT	Increased activation on the open-face emotions vs neutral faces contrast, after AT+ SCT in comparison to CG: - Left amygdala (d = 1.90) - Right amygdala (d = 1.51)
Luckhaus et al. (2013)	TAR	WG	RCT	Study quality rating of 2: randomization; gold-standard diagnostic criteria.	TAR = 10 WG = 6 §	EEG ERP	Pictures of Facial Affect Task (Ekman and Friesen 1976).	PFA-test; BFRT	Decreased activation at 172 msec after TAR: - Left inferior parietal lobe - Left temporal lobe (fusiform gyrus and middle occipital gyrus) Increased activation at 250 msec after TAR: - Right superior and middle frontal gyrus - Right anterior cingulate

Table 4 (continued)

Study authors	Treatment condition	Control condition	Study design	Methodological quality ratings (1–5)	Sample included for Analysis	Imaging method	Experimental task	Social Cognition outcome measures	Neuroplastic Findings
Mazza et al. (2010)	ETIT	PST	RCT	Study quality rating of 3: randomization, gold-standard diagnostic criteria, active control.	ETIT = 16 PST = 17	ERP	Emotion recognition task (Ekman 1993).	AToMS; Emotion Attribution Task; EQ	No major findings described. N200 amplitude higher in the ETIT group during anger emotion response.
Popov et al. (2015) †	FAT	BFP TAU	RCT	Study quality rating of 3: randomization; gold-standard diagnostic criteria; active control.	FAT = 19 BFP = 19 TAU = 19	MEG	Paired-click task (as described by the authors)	N/a	No significant changes in oscillatory brain dynamics after FAT. Significant changes were found on the BFP group.
Popova et al. (2014) †	FAT	CE TAU	RCT	Study quality rating of 3: randomization; gold-standard diagnostic criteria; active control.	FAT = 19 CE = 19 TAU = 19	Not reported	Facial affect recognition task (Popov et al. 2013; Popov et al. 2014).	MSCEIT; FAR	Decreases in alpha power modulation after TAR in contrast to a non-significant decline in the TAU group (*d = 0.729)*
Stroth et al. (2015)	TAR	HC	Controlled intervention Design	Study quality rating of 1: gold-standard diagnostic criteria.	TAR = 12 HC = 14	EEG ERP	Affect recognition task (Lundqvist et al. 1998).	BFRT	ERP P60 amplitude significantly increased after TAR in two central sites: - Parietal electrodes: (*d = 0.800)* - Occipital electrodes: (*d = 0.620)* sLORETA analysis revealed increased activation in 60 ms in several brain regions after TAR: - Inferior Parietal Lobule (*d = 1.77)* - Precuneus (*d = 1.77)* - Superior Parietal Lobule (*d = 1.869)*
Subramaniam et al. (2012) ‡	SZ-AT	SZ-CG	RCT	Study quality ratings of 4: randomization; blinded raters; gold-standard diagnostic criteria; active control.	SZ-AT = 15 SZ-CG = 14 **	fMRI	Reality monitoring task (Vinogradov et al. 2008).	N/a	Increased medial prefrontal cortex activity after intervention in the SZ-AT group in comparison to the SZ-CG (*d = 0.777)*
Subramaniam et al. (2014) ‡	SZ-AT	SZ-CG	RCT	Study quality ratings of 4: randomization; blinded raters; gold-standard diagnostic criteria; active control.	SZ-AT = 15 SZ-CG = 13 **	fMRI	N-back working memory task (as described by the authors)	N/a	Increased activity after intervention in the SZ-AT group in comparison to the SZ-CG - Left middle frontal gyrus - Left inferior frontal gyrus

*These studies ran in parallel; † The samples from these studies may share some participants; ‡ These studies used the same sample and training procedures, but different experimental tasks; § At 2 months follow-up WG = 5; ** At 6 months follow-up SZ-AT = 13 and SZ-CG = 12

CET = Cognitive Enhancement Therapy; EST = Enriched Supportive Therapy; RCT = Randomized controlled trial; MRI = structural magnetic resonance imaging; MSCEIT = Mayer – Salovey – Caruso – Emotional Intelligence Test; TAR = Training of Affect Recognition; TAU = treatment as usual; fMRI = functional magnetic resonance imaging; AT + SCT = Auditory-based cognitive training plus social cognition training; CG = computer game; WG = Waiting Group; EEG = electroencephalography; ERP = event-related potentials; PFA-test = Prototypical facial expressions; BFRT = Benton Face Recognition Test; ETIT = Emotion and ToM Imitation Training; PST = Problem Solving Training; AToMS: Advanced Theory of Mind Scale; EQ = Empathy Questionnaires; BFP = Brain Fitness Program; FAT = Facial Affect Recognition Training; MEG = magnetoencephalography; CE = cognitive exercises; FAR = facial affect recognition task; HC = healthy controls; SZ-AT = active computerized cognitive training; SZ = schizophrenia

emotion percpetion and post-intervention activation increases on open-face emotions contrast in the right amygdala (r = 0.45), medial PFC cortex (r = 0.43) and right putamen (r = 0.44), with a trend towards statistical significance in the left amygdala (r = 0.39).

Subramaniam et al. (2012) and Subramaniam et al. (2014) delivered the same broad-based SCT protocol composed of intensive computer-based cognitive, FER and ToM exercises. However, each trial used different experimental tasks to compare fMRI measures with a CG that completed regular computer games. Subramaniam et al. (2012) used a reality monitoring task and found increased medial PFC cortex activity after intervention in the SCT group in comparison to the CG (d = 0.777). It is also important to note that the authors did not report data regarding whole-brain analysis and used only the medial PFC region of interest. Post-experimental behavior measures of reality monitoring were also correlated with post-experimental activation in the medial PFC only for patients in the SCT group (r = 0.53). Furthermore, medial PFC activity after training was also significantly correlated with social functioning six months later (r = 0.55). Subramaniam et al. (2014) used an N-back experimental task and found significant increases in the SCT group in comparison to controls in the left inferior and middle frontal gyrus. The authors did not report sufficient data for effect size calculation. The authors did not use any social cognitive measures, but they reported a strong association between improved working memory performance (on the 2-back task) and changes in right medial frontal gyrus activation (r = 0.69) in the SCT group. In the SCT group, occupational functioning at 6-month follow up was also significantly associated with left and right medial frontal gyrus activity after training (r = 0.57; r = 0.58, respectively).

ERP and EEG

Only two studies selected for this review used a combination of ERP and EEG imaging methods (Luckhaus et al. 2013; Stroh et al. 2015). Both utilized SCT programs targeting FER using both computer and pen & pencil exercises, although they used different experimental tasks to assess brain changes. Luckhaus et al. (2013) used pictures of the facial affect task from Ekman and Friesen (1976) and found that ERPs remained unchanged post- vs. pre-intervention. Standardized Low Resolution Electromagnetic Tomography Brain (LORETA) analysis showed decreased activation in the left inferior parietal lobe and left temporal lobe at 172 msec and increased activation in the right superior and middle frontal gyrus and anterior cingulate at 250 msec. The authors did not present sufficient data to compute effect sizes. Stroh et al. (2015) used the Karolinska Directed Emotional Faces picture set (Lundqvist et al. 1998), but compared neural activity outcomes using a healthy CG. ERP results showed significantly increased P60 amplitude after training in parietal eletrodes (d = 0.80) and occipital electrodes (d = 0.620). LORETA analysis found a significant increase activation in the inferior and superior temporal lobe (d = 1.77; d = 1.869, respectively) and in the precuneus (d = 1.77) at 60 ms.

ERP

Mazza et al. (2010) conducted the only study measuring neuro-physiological activation using only ERP. Researchers used the emotion recognition task from Ekman (1993) to compare the effects of Emotion and ToM Imitation Training in comparison to an active CG. The authors did not find any group vs time interaction, but they reported main effects of group on N200 amplitude ($p < 0.001$). Thereby, N200 amplitude was significantly higher in the SCT group (mean = −4.65 mV) in comparison to the active CG (mean = −2.24 mV).

MEG

Two studies used MEG as the imaging method (Popova et al. 2014; Popov et al. 2015) and both compared a TAU group with a computer-based SCT program targeting FER with an auditory verbal discrimination and memory training protocol. Popov et al. (2015) used a paired-click task as the experimental task and found no significant alpha power response changes in the SCT or TAU groups (d = 0.12; d = 0.52, respectively), while the cognitive training group demonstrated a significant decrease in alpha power response (d = 0.84). In the other MEG study, Popova et al. (2014) used a FER experimental task and found an alpha power modulation increase in the SCT group in comparison to a non-significant decline in the TAU group (d = 0.729). Also, in the SCT group alpha power increase in the left fronto-central sensor cluster was significantly associated with blended emotion task performance (r = 0.46).

Discussion

Neurobiological models of social cognition implicate an extended neural system that comprises a wide range of highly intertwined, but specialized networks that allow for intact social behavior, affective response capability and emotion processing (Brunet-Gouet and Decety 2006; Burns 2006, 2004; Fujiwara et al. 2015; Pinkham et al. 2003). Schizophrenia is characterized by changes in neuronal circuits connecting cortical and subcortical structures which integrate the social brain (Habel et al. 2010a; Martin et al. 2014; Brunet-Gouet and J. Decety 2006; Lee et al. 2004). To our knowledge this is the first systematic review that specifically examines the neuroplastic effects of SCT in patients with schizophrenia. With the exception of Popov et al. (2015) and Mazza et al.

(2010), every reviewed study reported significant changes in structural or functional brain regions that have been linked to social cognition. We will discuss how SCT affects specific regions within the social brain and consider several hypotheses about how these networks come together, providing a neural system perspective regarding the possible targets of SCT.

Early Processing and Perception of Social Stimuli

The visual pathway is the most widely studied early processing modality, as many areas known to detect biological information such as faces and bodies are located within the visual system and the temporal cortex (Grossman and Blake 2002; Astafiev et al. 2004; Cazzato et al. 2015). There is clear evidence suggesting that visual areas such as the fusiform gyrus, the inferior occipital gyrus and the posterior superior temporal sulcus play a role in the early perceptual processing of facial stimuli (Gobbini and Haxby 2007; Fox et al. 2009; Fusar-Poli et al. 2009). The occipital face area is responsible for the early processing of faces, subsequently transferring information to the temporal regions, where the posterior superior temporal sulcus is responsible for processing changeable aspects of face perception (Ishai et al. 2005) and the fusiform gyrus for encoding invariant facial features and early categorization of facial expressions (Tsuchiya et al. 2008; Pizzagalli et al. 2002). In schizophrenia, several meta-analyses of fMRI studies have found reduced activation in the fusiform gyrus and the inferior and middle occipital gyrus during FER (Delvecchio et al. 2013; Li et al. 2010; Sugranyes et al. 2011), suggesting a global impairment in visual perception which in turn hinders facial stimuli processing (Green et al. 2011).

In our review, Eack et al. (2010) utilized a broad-based SCT program that reduced gray matter volume loss in the fusiform gyrus of patients with schizophrenia, although they reported small effects of treatment ($d = 0.247$). Luckhaus et al. (2013) found reduced activation after training in regions mainly involved in the automatic processing of facial emotions (superior temporal, fusiform and middle occipital gyrus), suggesting increased efficiency of the structural face processing network through the use of compensatory learning strategies. Contrastingly, Habel et al. (2010b) found extensive activation in regions critical to perception (posterior parietal and occipital cortex) after training, suggesting that perceptual strategies may have normalized the activity of visual regions. Interestingly, these two trials applied similar training protocols but their discrepant findings regarding early processing regions activation may be related to the methods used to gather neurofunctional information.

Several authors have argued that the mirror neuron system is critical to the ability to identify and understand other people's emotions (Uddin et al. 2007; Keysers and Gazzola 2007). Neuroimaging studies suggest that this system involves a complex interaction between the superior temporal sulcus, the inferior frontal gyrus, the premotor cortex and the inferior parietal lobe, even extending to regions in the superior parietal lobe (Van Overwalle 2009). Two of the studies included in this review suggested that the involvement of the mirror system was related to SCT-induced neurofunctional changes and reported moderate to large effect sizes ($d = 0.8$–2.10) on relevant brain regions including the postcentral gyrus, the parietal lobe and the superior temporal gyrus (Hooker et al. 2012; Stroth et al. 2015). The postcentral gyrus mediates somatosensory experience and may facilitate FER by simulation processes. The superior parietal lobe is activated during the observation of detailed aspects of motor action, and improvements in this area may be related to increased patient's ability to focus on salient facial features such as eyes and mouth (Molenberghs et al. 2010). As such, after training patients may be able to adopt visual exploration strategies that allow serialized screening procedures of specific face regions in order to identify emotions.

Temporoparietal Junction and the Mentalizing Network

The temporoparietal junction extends from the superior temporal sulcus to the inferior parietal lobe and has been systematically associated with ToM tasks requiring participants to make inferences about others' intentions, and affective or cognitive states based on their behavior (Saxe and Kanwisher 2003; Saxe and Powell 2006; Van Overwalle 2009). There is evidence that patients with schizophrenia recruit the same networks for ToM as healthy controls (Bosia et al. 2012) in spite of displaying reduced temporoparietal junction activity when performing these tasks (Benedetti et al. 2009; Walter et al. 2009). In this review, while some authors reported SCT-induced changes in the activity of the superior temporal sulcus or the inferior parietal lobe (Habel et al. 2010b; Luckhaus et al. 2013; Stroth et al. 2015; Hooker et al. 2012), none of the studies specifically described significant results on the temporoparietal junction cluster. This is most likely because almost all studies used FER tasks to explore SCT-induced neuroplastic effects. Although temporoparietal regions have been implicated in facial emotion processing (Fusar-Poli et al. 2009), several meta-analyses with patients with schizophrenia found no activation changes during FER task performance (Delvecchio et al. 2013; Li et al. 2010; Sugranyes et al. 2011). Since none of the authors used any kind of ToM experimental task or an intervention protocol specially focused on ToM, it would be very unlikely to observe any changes in temporoparietal junction activity.

The Limbic System and Social Stimulus Evaluation

Limbic areas play a clear role in social cognition, specially contributing to facial emotion processing (Arnold 2016). Several limbic structures (anterior insula, cingulate and

parahippocampal gyrus) have been linked to FER, but the most frequently studied structure has been the amygdala. The amygdala plays a critical role in classifying stimuli as salient as well as judging other people's faces (Adolphs 2009), and as such is essential to understanding others' emotional states (Morris et al. 1998; Whalen et al. 1998). Several meta-analyses concluded that patients with schizophrenia display impaired activation in the amygdala and parahippocampal gyrus when processing facial emotions (Li et al. 2010; Sugranyes et al. 2011; Anticevic et al. 2012). When contrasting emotional and neutral facial expressions, patients with schizophrenia show reduced activation of the amygdala in comparison to healthy controls, which apparently hinders their performance in FAR tasks (Delvecchio et al. 2013).

In our review only two authors reported structural or functional changes in the amygdala after SCT training, with effect sizes ranging from small to large (d = 0.287–1.90). Eack et al. (2010) reported that a 2 year broad-based SCT program produced structural changes in several limbic structures from the left medial temporal lobe including the hippocampus, parahippocampal gyrus and amygdala, although main treatment effects were small to moderate (d = 0.243–0.310). Patients displayed increased gray matter volume in the left amygdala and reduced neurodegeneration in other limbic regions. Keshavan et al. (2011) also found that a higher baseline gray matter volume in the temporal cortex predicted social-cognitive response after training, which further supports the role of the limbic system in the neural circuits targeted by SCT.

Hooker et al. (2013) found increased bilateral activation in the amygdala following an intervention combining auditory training with SCT, but only in response to open-mouth expressions (happiness, surprise, and fear). The authors postulated that SCT may have increased the allocation of arousal and effective attentional resources only to salient facial characteristics displayed in expressions related to potential threats, rewards or unexpected events (e.g. eyes wide open in fear). There is strong evidence that happy and fearful faces activate the amygdala bilaterally, while sad faces show a laterality effect, and angry or disgusted faces do not have an effect in this region (Fusar-Poli et al. 2009). Hooker et al. (2013) did not find significant changes in amygdala activity after SCT for angry, sad and disgust facial expressions. It is possible that the amygdala is only maximally responsive to specific emotions, which may explain why several trials did not report significant changes in its activity. For instance, Habel et al. (2010b) only contrasted sad and happy faces to neutral faces, making it less likely to detect activation changes than if if they had included fear and surprise stimuli. Furthermore, several of the included studies did not even use any kind of social cognitive task, making it even less likely to observe SCT-induced changes in amygdala activation (Popov et al. 2015; Subramaniam et al. 2012; Subramaniam et al. 2014).

Prefrontal Regions and Complex Social-Cognitive Mechanisms

The role of the prefrontal areas in social cognition has been extensively explored by researchers - the PFC seems to be involved in the processing of long-term traits of the self and others, as well as interpersonal knowledge of norms and scripts (Uddin et al. 2007; Keysers and Gazzola 2007). Furthermore, the medial PFC seems to play a role in ToM, including complex and explicit meta-representations (Van Overwalle 2009), as well as on conscious experience of emotion, inhibition of excessive emotion, monitoring one's own emotional state to make relevant decisions and FER (Fusar-Poli et al. 2009). In patients with schizophrenia, there is an under activation of the medial PFC during ToM tasks (Sugranyes et al. 2011) and reduced activation of the inferior (Sugranyes et al. 2011), medial (Delvecchio et al. 2013) and superior (Li et al. 2010) frontal regions during FER tasks.

In our review there were three fMRI studies and one EEG study that reported increased activity after SCT in the inferior, medial and/or superior frontal gyrus, although effect size calculation was only possible for Subramaniam et al. (2012), which demonstrated a moderate to large main effect of treatment (d = 0.763). Luckhaus et al. (2013) reported increased superior and middle frontal activation after training, suggesting a shift from a reflexive to a more reflective strategy of emotional face processing as the patients developed prefrontal dependent compensatory strategies in order to improve performance. However, the trials from Subramaniam et al. (2012) and Subramaniam et al. (2014) combined auditory and visual processing exercises with ToM and FER training, which does not allow to conclude that prefrontal changes were caused by specific SCT elements. Cognitive training can lead to increased dorsolateral PFC activity and working memory improvement (Haut et al. 2010; Edwards et al. 2010), an effect that may potentiate SCT efficacy. Moreover, the changes reported by Habel et al. (2010b) were very similar to the results reported by cognitive remediation studies which suggest general rather than specific intervention effects (Wykes et al. 2011). SCT-induced neural changes may rely on the enhancement of cognitive, attentional and perceptual processes, which are important but non-specific to social cognitive processes.

Can SCT Change Social Brain Networks?

Social neuroscience research has revealed that the social brain includes several neural systems comprising complex neural interconnections between cortical regions and deeper structures of the limbic system (Burns 2006, 2004). The ToM or mentalizing network encompasses a complex interaction between the bilateral temporoparietal junction, the medial PFC the posterior cingulate cortex and the amygdala (Siegal and

Varley 2002; Adolphs 2003). Regarding FER, there is an influential theory emphasizing the combined role of the core system (occipital and temporal lobes) and the extended system, which ranges from the middle superior temporal sulcus through the amygdala and into the PFC (Gobbini and Haxby 2007; Fox et al. 2009).

Upon examination of these complex networks, it is clear that social cognition encompasses an interaction between perceptual regions, associative areas that affectively or cognitively label external stimuli, and structures that evaluate social information and create higher-order mental inferences about others and the world. As such, understanding the role of isolated structures becomes less important, and the need to increase our focus on connectivity and neural circuits that underlie social cognitive processes becomes more pressing (Stanley and Adolphs 2013).

In spite of the the several training and imaging procedure discrepancies within the studies included in our review, there was a wide-range of neuroplastic training effects in distinct regions, with effect sizes mostly ranging from moderate to large. SCT may trigger a varied set of rehabilitative mechanisms that specifically target impaired emotion-processing networks, but we are still far from fully understanding which components are responsible for the reported brain changes. Perhaps broad-based programs combining neurocognitive and social cognitive exercises allow patients to develop alternative strategies when assessing social stimuli, increasing activation in prefrontal regions which subsequently produces changes in limbic structures such as the amygdala. The ventral PFC has a regulatory influence on the amygdala and other posterior cortical regions, and may modulate social stimulus processing after SCT training (Quirk and Beer 2006; Ochsner et al. 2012). Conversely, targeted SCT programs addressing only FER may stimulate more perceptive brain regions as patients gradually become more effective in detecting and classifying facial features using procedural visual screening methods.

It is also important to note that almost all of the included studies reported significant associations between behavioral improvements and neuroplastic changes except Popova et al. (2014). We cannot definitively state which SCT mechanisms produce brain changes, as there is great variability in the regions showing intervention effects across studies, but it seems clear that SCT-induced changes within the social brain are related to social cognitive performance. However, the question still remains: can brain activity modified by training lead to enhanced social cognitive performance, or do the compensatory strategies suggested by SCT improve patients' social cognitive proficiency and abilities, which in turn induces changes in the social brain?

Efforts to find convergent neuroplastic findings induced by SCT are hindered by several factors. First, the characteristics of neuroimaging procedures are critical to detect intervention effects, as each region may be maximally responsive to specific elements of social cognition. Some of the included trials used working memory, paired-click, or reality monitoring tasks, which may not be ideal to capture changes in areas relevant to social cognition. Most studies actually used FER tasks rather than ToM or any other kind of social cognitive task, which could also be more effective alternatives for finding training effects, especially in broad-based or comprehensive SCT protocols. Moreover, there was a wide disparity in the emotion stimuli and categories used in FER tasks, which can clearly generate different brain activation patterns.

Second, we included studies that used several different methods to measure structural and functional brain changes, which makes the results difficult to directly compare. Even within the fMRI studies, data analysis and processing varied across studies, as some authors did not apply any kind of correction procedure, did not perform whole-brain analyses (only regions of interest) and did not present any kind of control task not associated with social cognitive performance.

Third, there are substantial differences between the SCT programs used in the included studies, which makes it difficult to identify the components responsible for the neural changes. For instance, there is a lack of studies assessing the effects of comprehensive SCT programs. Most of the studies chose SCT protocols that targeted specific domains of social cognition such as FER. Training programs also varied in duration, intensity and contact time with the health professionals, which can significantly influence outcome measures.

Limitations of the present review also include the small number of studies conducted to date, as well as several within-study biases. The small number of subjects in both treatment and control groups contribute to an increased risk of Type II error due to the low statistical power. This may explain why many brain areas linked to the social cognitive system were not related to social cognitive changes. Moreover, some trials did not report blinding procedures, description of fidelity maintenance and active control conditions. Baseline differences between participants from the active treatment and control groups were also common.

Conclusion

The present review clearly suggests that social brain networks of patients with schizophrenia can be modified by SCT, emphasizing its importance in the treatment of these disorders. Using different functional and structural brain measurement methods, the included studies indicate that neural changes induced by SCT are measurable and are transferrable to social cognitive outcomes. Future research should investigate possible neural changes from broad-based, comprehensive or targeted SCT interventions directed towards other areas of social cognition such as ToM, attributional style and social

perception. Additionally, studies examining the durability of training-induced neuroplastic effects are needed in order to show that SCT can confer long-term benefits on individuals with schizophrenia, even after the completion of treatment. Researchers should also take into the account the appropriateness of the tasks chosen to evaluate changes in social cognitive networks, as each area of the social brain may be maximally activated by distinct experimental paradigms. There is still a need for more randomized clinical trials with standardized evaluation methods and intervention programs, blinding procedures, descriptions of fidelity maintenance, inclusion of active control conditions, and consistency regarding active treatment and CG sample size, in order to obtain clear results that can be generalized to the target clinical population. Given that SCT has the ability to induce neuroplasticity changes and that most neural and social cognitive impairments are present before illness onset, clinical trials should explore its effectiveness in the early or prodromal phase of the disease when the potential for neuroplastic changes is likely higher in children and adolescents. The mechanisms by which SCT is effective are still unknown, but while pharmacological interventions display little efficacy in the treatment of social cognitive impairments, specialized SCT programs seem to be a valuable alternative to promote social cognitive improvements accompanied by neuroplastic changes in the social brain.

Compliance with Ethical Standards

Conflict of Interest The author(s) confirm that this article content has no conflicts of interest.

Appendix 1. Measures Used in the studies

Social Cognitive Measures

Emotion Perception

- Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT: Perceiving Emotions subtest) (Mayer, Salovey, Caruso, & Sitarenios, 2003)
- Emotion discrimination task (Habel et al., 2010)
- Pictures of Facial Affect (PFA) (Ekman and Friesen 1976)
- Benton Face Recognition Test (BFRT) (Benton, 1994)
- Emotion attribution task (Blair & Cipolotti, 2000; Mazza et al., 2007)
- Facial affect recognition task (Popova et al. 2014)

Theory of Mind

- Advanced Theory of Mind Scale (Happé, 1994)

Social function

- Empathy Questionnaires (EQ) (Baron-Cohen & Wheelwright, 2004)
- Social Performance Scale (PSP) (Morosini, Magliano, Brambilla, Ugolini, & Pioli, 2000)

Neurocognition Measures

- Wechsler Memory Scale (WMS) (Wechsler, 1987)
- Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1981)
- California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987)
- Wisconsin Card Sorting Test (WCST) (Heaton, Chelune, Talley, Kay, & Curtiss, 1993)
- Tower of London (Culbertson & Zillmer, 2001)
- Trail Making Test part B (TMT-B) (Reitan, 1992; Reitan & Wolfson, 1985)
- Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999)
- Matrics Consensus Cognitive Battery-Composite (MCCB) (Nuechterlein et al., 2008)
- RAVEN-Matrizen-test, standard progressive matrices (Heller, Kratzmeier, & Lengfelder, 1998)
- Forward and Backward Digit Span (Evans, Chua, McKenna, & Wilson, 1997)
- Trail Making Test part A (TMT-A) (Reitan, 1992; Reitan & Wolfson, 1985)
- Rey Auditory Verbal Learning Test (RAVLT) (Evans et al., 1997)
- Behavioural Assessment of the Dysexecutive Syndrome (BADS) (Evans et al., 1997)
- Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004)
- Neuropsychological Assessment Battery (NAB) (Stern & White, 2003)

Symptoms

- Positive and Negative Syndrome Scale (PANSS) (Kay, Flszbein, & Opfer, 1987)
- Psychopathy Check List: Short Version (PCL:SV) (Hart & Cox, 1995)
- Historical Clinical and Risk Management Scales (HCR-20) (Müller-Isberner, Jöckel, & Gonzalez Cabeza, 1998)
- Brief Psychiatric Rating Scale (BPRS) (Ventura et al., 1993)

Functioning

- Global Assessment of Functioning (GAF) (American Psychiatric, 2000)
- Quality of life scale (QLS) (Bilker et al., 2003)

Other Measures

- Neurological Evaluation Scale (NES) (Buchanan & Heinrichs, 1989)
- Edinburgh Handedness Questionnaire (EHQ) (Oldfield, 1971)

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