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Converging Effects of Diverse Treatment Modalities on Frontal Cortex in Schizophrenia: A Review of Longitudinal Functional Magnetic Resonance Imaging Studies

Ayşe Sakalli Kani¹, Ann K. Shinn², Kathryn E. Lewandowski², and Dost Öngür²

¹Sivas Numune State Hospital, Department of Psychiatry, Sivas, Turkey.

²Psychotic Disorders Division, McLean Hospital, 115 Mill St., Belmont, MA 02478, USA; Harvard Medical School, Department of Psychiatry, Boston, MA 02114, USA.

Abstract

Objectives—A variety of treatment options exist for schizophrenia, but the effects of these treatments on brain function are not clearly understood. To facilitate the development of more effective treatment strategies, it is important to identify how brain function in schizophrenia patients is affected by the diverse therapeutic approaches that are currently available. The aim of the present article is to systematically review the evidence for functional brain changes associated with different treatment modalities for schizophrenia.

Methods—We searched PubMed for longitudinal functional MRI (fMRI) studies reporting on the effects of antipsychotic medications (APM), repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), cognitive remediation therapy (CRT) and cognitive behavioral therapy for psychosis (CBTp) on brain function in schizophrenia.

Results—Thirty six studies fulfilled the inclusion criteria. Functional alterations were observed in diverse brain regions. Across intervention modalities, changes in fMRI parameters were reported most commonly in frontal brain regions including prefrontal cortex, anterior cingulate and inferior frontal cortex.

Conclusions—We conclude that current treatments for schizophrenia commonly induce functional brain alterations in frontal brain regions. However, interpretability is limited by inconsistency in task and region of interest selection, and failures to replicate. Further task independent fMRI studies examining treatment effects with whole brain analysis are needed to deepen our insights.

Keywords

schizophrenia; fMRI; antipsychotic; rTMS; tDCS; CRT; CBTp; brain function

Corresponding Author: Dost Öngür, McLean Hospital/Harvard Medical School, 115 Mill St. Belmont MA 02478. Tel. : +1 (617) 8553922. dongur@partners.org.

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1. INTRODUCTION

Schizophrenia is a disabling mental disorder, the etiology of which remains elusive (1). Antipsychotic medications (APM), the mainstay of treatment, are relatively effective at improving the positive symptoms of this condition, but they are less effective in treating negative (2) and cognitive symptoms (3), the best predictors of functional outcome, often do not produce sustained recovery (4), and are associated with a number of serious side effects. There is an urgent need for more effective treatments.

Non-pharmacological approaches are also commonly used to treat schizophrenia and include talk therapies like cognitive behavioral therapy for psychosis (CBTp). CBTp teaches patients to self-monitor thoughts and question the evidence supporting abnormal beliefs. It also teaches ways to cope with the distress caused by persistent psychotic symptoms (5). CBTp has been shown to improve positive and negative symptoms (6, 7), adherence to treatment (8), depression (9) and insight in patients with schizophrenia (10).

In addition, more novel treatment strategies such as cognitive remediation therapy (CRT) and avatar therapy, and non-invasive brain stimulation techniques, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have been applied in an attempt to ameliorate cognitive deficits and other psychosis symptoms resistant to APM. CRT, a behavioral intervention that aims to improve cognitive deficits via repeated behavioral training (11), has been shown to enhance cognitive performance and psychosocial functioning in patients with schizophrenia (12-14). rTMS, which involves non-invasive electromagnetic stimulation of specific brain areas (15), has been applied to the treatment of auditory hallucinations (16-20), working memory (WM) (21) and negative symptoms (15). tDCS is another non-invasive neurostimulation technique that modulates brain activity via a low-intensity electric current applied directly to the head through scalp electrodes (22). Studies using tDCS have demonstrated improvement in cognitive performance (23) and reduction in auditory hallucinations in schizophrenia (24).

Despite the increase in the number of therapeutic options available and/or emerging, it remains unclear what effect these treatments have on the brain. Yet, in order to develop more targeted and effective therapies for schizophrenia, it is crucial to recognize the effects of current treatments on brain function (25). Indeed, the NIMH has recently shifted focus of clinical trials for both pharmacological and non-pharmacological interventions to an experimental therapeutics approach (26), which emphasizes evaluation of the potential for a treatment to engage a hypothesized target (e.g. neural circuits) rather than studying efficacy of a treatment whose mechanisms have not yet been clearly established.

Functional neuroimaging is one approach that enables observation of the functional alterations that can occur with a treatment in clinically-relevant timescales (25). Among the techniques in this category, single photon emitted computed tomography (SPECT) and positron emission tomography (PET) have been used to identify changes in brain function, blood flow, metabolism and neuroreceptor and neurotransmitter activity due to drug treatments (27). Another approach, functional magnetic resonance imaging (fMRI) can be used to measure changes in the blood oxygen level dependent signal, an indicator of

neuronal activity and brain function (28). Task-dependent fMRI investigations measure changes in brain activity by detecting BOLD signal alterations during the performance of specific tasks. Functional connectivity (FC) during task-independent fMRI can identify intrinsic networks, which demonstrate synchronous low-frequency (<0.1 Hz) BOLD oscillations during resting-state. FC reflects the level of integration across brain regions, and can provide insight into the "dysconnectivity" or disintegration of brain networks in schizophrenia (29-31). As a noninvasive and relatively safe tool for investigating *in vivo* brain function with high spatial resolution, fMRI can be used to measure the biological effects of candidate treatment strategies, and may provide a useful biomarker in clinical trials (29, 32). The promise of these approaches have been demonstrated in recent work indicating that functional connectivity of the striatum can predict response to APMs in first episode psychosis (33) and that striatal activity during reward anticipation predicts weight gain in response to subsequent APM therapy (34).

In the current paper, we aimed to review functional brain changes associated with currently available treatments for schizophrenia, and, more specifically, to identify whether there are any treatment-related functional brain changes that the diverse approaches have in common. We did not find any clinical trials evaluating the impact of CRT, rTMS, tDCS and avatar therapy with PET or SPECT, so we review only longitudinal fMRI studies which address the impact of various treatment modalities in patients with schizophrenia. We present our analysis for each modality in order (and in associated Tables). For each modality, we consider resting state FC, FC during task activation, and regional brain activation during tasks in order because these represent related but distinct aspects of brain activity. We then provide a summary of our observations at the end of each modality section. In the Discussion section, we summarize our findings and synthesize the information to provide a perspective for the reader. We conclude that functional changes are observed in frontal cortex across treatment modalities, which we hypothesize are related to known brain abnormalities in schizophrenia. In this process, we also highlight the sources of heterogeneity in this literature as well as the limitations inherent in fMRI approaches.

2. METHODS

We performed a systematic search of longitudinal schizophrenia studies utilizing fMRI methods in the PubMed database, using logical combinations of the following terms: "schizophrenia," "psychosis," "functional magnetic resonance imaging," "fMRI," "antipsychotic treatment," "transcranial magnetic stimulation," "transcranial direct current stimulation," "avatar therapy," "cognitive remediation therapy" and "cognitive behavioral therapy". The bibliographies of the published papers were also examined and pertinent studies included. We found 50 articles, spanning from August 1999 to April 2016. The inclusion criteria for the studies were: (a) publication in English; (b) inclusion of patients with schizophrenia or psychosis; (c) inclusion of fMRI outcome measures; (d) comparison of functional brain changes pre- and post-intervention. We excluded two APM papers (35, 36) due to the lack of meaningfully defined pre-treatment conditions (too diverse a representation of APM's), which make interpretation of the results difficult. We excluded investigations evaluating: 1) the effects of one session of cognitive training on brain function (not longitudinal) (37) and 2) baseline functional abnormalities in patients which predicted

treatment outcome (38-40). (See Figure 1 for details regarding literature search and study selection). We focused on the results of the interventions in patients, rather than differences between patients and healthy controls and on findings which are statistically significant or emphasized by the authors. One study reported both the functional brain changes after one session and repetitive sessions of tDCS, we included only the findings after overall treatment(41). Finally, one of the studies (42) used three imaging techniques, but we included only the fMRI findings in the present paper.

3. RESULTS

A total of 36 investigations were included in this review. Seventeen studies assessed changes in functional brain activity related to APM (33, 43-58), 5 studies measured the effects of rTMS (59-63), 10 studies evaluated the effects of CRT (42, 64-72), two studies measured functional brain changes following CBTp (73, 74), and two studies measured functional brain changes following tDCS (41, 75). To our knowledge, there are no studies examining the effects of avatar therapy on brain function using fMRI. See Tables 1-4 for the details of included studies. Note that in these tables the sample size we report is the one included in the imaging analyses and not the overall sample size.

3.1. Functional brain changes associated with APM

3.1.a. The effects of APM on resting state functional connectivity—Six APM studies were conducted using resting state analyses. Lui and colleagues examined changes in brain function at rest in 34 APM naïve patients before and after six weeks of second generation antipsychotic (SGA) treatment (44) determined naturalistically. The investigators found an increase in amplitude of low frequency fluctuations (ALFF) in nine brain areas, including right middle frontal gyrus, left superior frontal gyrus, right inferior frontal gyrus (IFG), bilateral medial frontal cortex, right inferior parietal lobule (IPL), left superior parietal lobule (SPL), left superior temporal gyrus, and right caudate nucleus. The increases in ALFF correlated with clinical improvement in positive but not negative symptoms. There were also significant FC reductions between 7 of the 9 ALFF-based seeds and widespread cortical and subcortical brain areas (there were no significant FC abnormalities involving the left superior frontal gyrus and left SPL seeds). Independent component analysis revealed reduced FC in four networks including the temporal-parietal, occipital-basal ganglia, precuneus-basal ganglia, and temporal-frontoparietal networks.

Hadley and colleagues investigated the FC of the ventral tegmental area (VTA)/midbrain, the origin of the mesocorticolimbic dopamine projections, before and after one week of treatment with risperidone (flexible dosing; mean dose not reported) to determine whether VTA-seeded FC after just one week of medication could predict clinical response after a full 6 weeks of treatment (43) and discovered that the VTA/midbrain connectivity to bilateral regions of the thalamus increased with one week of medication treatment. Sarpal and colleagues investigated the effects of SGA treatment in first episode psychosis patients on 12 striatal subregions (33). The authors found increased FC between the right dorsal caudate seed and prefrontal areas [anterior cingulate, right dorsolateral prefrontal cortex (DLPFC), and right orbitofrontal cortex], and decreased FC between two striatal seed regions (right

ventral caudate/nucleus accumbens and left ventral caudate) and bilateral parietal regions as psychotic symptoms improved.

Li and colleagues examined whether resting state functional abnormalities in schizophrenia would be reduced after 1 year of antipsychotic treatment and whether these changes would be associated with the clinical improvement (58). After treatment with SGA (flexible dosing; mean dose not reported) the authors found an increase in ALFF values in right IPL and OFC and a decrease in right occipital gyrus. Also, these areas in which normalization was determined were defined as seed regions for FC analysis. Compared to baseline, there was an increase in FC between bilateral IPLs toward normal levels. Neither ALFF nor FC alterations were correlated significantly with the changes in clinical outcome measures.

Kraguljac and colleagues evaluated the resting state FC changes of posterior and anterior hippocampus, in response to six weeks of risperidone treatment (flexible dosing)(57). After treatment, the authors detected increased FC between the hippocampus and MPFC/ ACC, caudate and lingual gyrus. These alterations were correlated with clinical improvement. In another study, the same group also investigated resting state FC abnormalities in large scale functional networks (the dorsal attention network (DAN), executive control network, salience network, and default mode network) and examined subsequent changes with 6 weeks of risperidone (56). After treatment FC reductions were seen within the DAN, comprising the lingual gyrus, fusiform gyrus, precuneus, calcarine sulcus and cerebellum. However baseline connectivity in DAN was related to clinical response at six weeks, no correlation was reported between FC change and the improvement in clinical symptoms.

3.1.b. The effects of APM on functional connectivity during a cognitive task—

Sambataro and colleagues evaluated the effects of olanzapine monotherapy (mean daily dose 20 ± 6.9 mg) on FC within the default mode network (DMN) during performance of the N-back working memory (WM) task (55). After 8 weeks of olanzapine treatment, patients showed increased DMN FC strength in VMPFC compared to only 4 weeks of treatment.

3.1.c. The effects of APM on functional connectivity during a motor task—

Stephan and colleagues investigated the effects of olanzapine 10mg (n=4) or 15mg (n=2) on cerebellar FC in six schizophrenia patients via a seed-voxel correlation analysis (45). Compared to baseline, there was reduced left anterior cerebellar FC with a number of regions within prefrontal cortex (PFC) and mediodorsal thalamus. Right anterior cerebellar-seeded FC changes occurred throughout the brain. This study was limited by the very small sample size as well as by the fact that the researchers did not measure the clinical/behavioral response with olanzapine treatment.

3.1.d. The effects of APM on functional lateralization during a motor task—

Bertolino and colleagues examined the effect of olanzapine monotherapy on functional lateralization of sensorimotor cortex in 17 acutely psychotic schizophrenia patients who were either AP-naïve or AP-free for at least 4 weeks prior to study enrollment (46). The investigators calculated lateralization by measuring activity within manually drawn regions of interest (ROI's) of the primary sensory motor (PSM) cortex and premotor region in both hemispheres. Patients showed higher activation at eight weeks than at four weeks in the

contralateral primary sensory motor cortex, suggesting that some aspects of functional lateralization improved with clinical improvement although lateralization remained lower than in controls.

3.1.e. The effects of APM on brain activation during tasks of emotion

processing—Blasi and colleagues studied the effects of olanzapine on implicit and explicit processing of facial threatening stimuli in 12 acutely psychotic schizophrenia patients who were drug-naïve or drug-free for two weeks prior to study enrollment (47). Scans were acquired while patients matched angry or afraid faces (implicit processing), labeled target faces as either angry or afraid (explicit processing), or performed a sensorimotor control task. The authors had *a priori* hypotheses about left amygdala and PFC involvement, and found an interaction between diagnosis and time during both implicit and explicit processing in the left amygdala, and an interaction between diagnosis, time, and task in the right ventrolateral prefrontal cortex (VLPFC). Activation changes in left amygdala and right VLPFC were not correlated with symptom scores.

3.1.f. The effects of APM on brain activation during cognitive tasks—Honey and colleagues investigated the effect of substituting risperidone for typical APM on frontal cortical function, measured during a verbal working memory (WM) task (52). Twenty patients on stable doses of typical APM for at least one month were naturalistically assigned to two cohorts: n=10 patients continued to receive typical APM vs. n=10 were switched to risperidone after baseline assessment. While there were no significant changes in symptoms, as measured by the PANSS, over the six week period (the risperidone group showed a nonsignificant trend toward improvement), the authors found increased activation in right DLPFC, middle supplementary motor area (SMA) and posterior parietal cortex (bilateral precuneus) after risperidone treatment. A strength of this study is the presence of a typical APM control group; a weakness, however, is that patients were not randomly assigned to the two groups.

In a similar study design, Schlagenhauf and colleagues investigated whether olanzapine is superior to typical APM in improving DLPFC function, as measured by performance on the N-back task (51). After the switch to olanzapine, patients showed a significant increase in the DLPFC BOLD response during the attention (0-back) condition but not in the working memory (2-back) condition. The authors also found no significant change in the PANSS score between the two scans.

Snitz and colleagues conducted a naturalistic study to assess DLPFC and anterior cingulate cortex (ACC) function at illness onset and after treatment with second generation antipsychotics (SGA) (53). Participants were 11 drug naïve first episode patients and 16 healthy controls. The investigators used the Preparing to Overcome Prepotency task, designed to functionally dissociate the two regions. While patients showed hypoactivation in both DLPFC and ACC at baseline (compared to healthy subjects), 4 weeks after SGA treatment, patients displayed improved functioning (decreased hypoactivation) in the ACC, but not in the DLPFC. There was no correlation between change in symptoms and ACC or DLPFC activation.

Meisenzahl and colleagues evaluated the effect of steady state quetiapine on working memory (50). Schizophrenia patients showed increased activity in left VLPFC during the 2-back condition of the continuous performance task (CPT) after 12 weeks of SGA compared to baseline. Authors also reported an improvement in PANSS, Scale for the Assessment of Negative Symptoms (SANS), Clinical Global Impression (CGI) and BPRS scores after 12 weeks of treatment.

Keedy and colleagues used a visually guided saccade task to investigate the effects of APM on attentional and sensorimotor circuitry in 9 first episode schizophrenia (FES) patients with no or limited prior antipsychotic treatment (49). The authors found increased activity in bilateral supplementary eye fields, left frontal eye fields, and bilateral cerebellum, and decreased activity in a distributed network throughout the brain.

Van Veelen and colleagues investigated the effects of SGAs on brain functions during a Sternberg working memory task using ROIs that included the left fusiform gyrus, left and right superior parietal cortex, ACC and the left DLPFC (48). Based on the change in symptom ratings after APM, patients were divided into two groups as responder or non-responder. DLPFC dysfunction which was present at baseline did not change following APM. Similarly, there were no significant differences in other ROIs indicating that treatment response itself had no additional effect.

Recently Ikuta and colleagues evaluated the effects of risperidone and aripiprazole treatment on attentional control with the Multi-Source Interference Task (MSIT) (54). At baseline, patients demonstrated greater activation in the globus pallidus, and thalamus which were reduced after treatment. The authors reported positive correlations between the decrease in right globus pallidus activity and improvement in response accuracy and reductions in thought disturbance and unusual thought content, as assessed with BPRS. Patients also showed functional changes in other regions, including PFC areas, sensorimotor regions, occipital cortex, cerebellum, and brainstem after 12 weeks of treatment vs. baseline; however, these findings were not correlated with behavioral performance.

3.1.g. Summary: functional brain changes associated with APM—Our review of the 17 published longitudinal fMRI studies in the context of APM treatment reveals great diversity among studies in terms of patient populations, medication history and interventions, details of fMRI experiments (including field strength, and data collection/analysis/reporting), and focus on various aspects of behavior. We have presented these studies in Table 1, and have noted there some additional experimental details as well as a brief summary of the strengths and weaknesses of each study. We follow a similar format for each subsequent Table dedicated to the other modalities. Despite this diversity, we recognize certain patterns shared across studies. For example, nine of the 17 studies reported functional activation changes after APM and of these; 8 reported changes in frontal regions and change was always in the direction of more normal activity (when control data were present), or increased activation (46, 47, 49-54). Findings were reported in the DLPFC in three studies (49, 51, 52); in the VLPFC in two (47, 50); in the SMA in two (49, 52); and in the cingulate cortex in two (49, 53). Likewise, of the eight studies that reported effects of APM on FC, -six found FC changes with frontal regions including: SFG, MFG, IFG and

medial FG (44), cingulate cortex (33, 57) and DLPFC (33), orbitofrontal cortex (33, 45, 58), VMPFC (55), PFC (45, 57) and premotor cortex (45). 6/7 studies also reported subcortical FC changes.

As is often the case with neuroimaging studies, most reports we examined identified significant changes in multiple brain regions for each contrast. Therefore it is not possible for us to capture the richness of findings in each paper. Nonetheless, we noted that there were scattered findings also reported in the parietal, temporal, and occipital lobes in individual studies.

3.2. Functional brain changes associated with repetitive transcranial magnetic stimulation (rTMS)

3.2.a. The effects of rTMS on brain activity and auditory hallucinations—

Fitzgerald and colleagues examined the effects of rTMS on brain activity in regions related to language processing (left temporo-parietal cortex) in 3 patients with refractory auditory hallucinations (59). Patients were scanned during a word generation task known to activate primary and secondary auditory regions, within 48 hour before to initiation of rTMS and on the day following the end of the treatment course. After rTMS, the investigators found a reduction in hallucination severity in all three patients and found increased activation in left temporoparietal cortex (left angular gyrus), left superior parietal gyrus, left inferior parietal gyrus) and left frontal-precentral cortex (left middle frontal gyrus, left precentral gyrus). Recently, Kindler and colleagues measured the effects of rTMS on brain activity via pseudocontinuous magnetic resonance-arterial spin labeling (PCASL) (60). Thirty patients with medication-resistant auditory hallucinations were assigned randomly to receive rTMS to the left temporoparietal cortex or standard pharmacotherapy and scanned twice during a modified version of the language-processing task. After treatment, investigators found a decrease in cerebral blood flow (CBF) in the left primary auditory cortex (PAC), Broca's area, and in the cingulate gyrus. The PAC finding correlated with improvement in clinical assessments.

3.2.b. The effects of rTMS on functional connectivity and auditory

hallucinations—Vercammen and colleagues investigated the effects of 1 Hz rTMS on FC within auditory verbal hallucinations (AVH) related brain regions (61). Eighteen patients with medication-resistant AVH were scanned in the resting state and nine received rTMS to the left temporo-parietal junction. After rTMS, although no significant differences were observed in connectivity of primary ROIs, an increase in connectivity between the left temporo-parietal junction (TPJ) and the right insula was observed in the rTMS group.

3.2.c. The effects of rTMS on brain activation during a working memory task—

Guse and colleagues conducted the only study that assessed the effects of high frequency (10 Hz) rTMS on WM. Twenty five schizophrenia patients with predominant negative symptoms and 22 healthy controls all received high frequency active or sham 10 Hz rTMS over the left posterior middle frontal gyrus. There was no statistically significant activation change during a letter 2-back task in the working memory network over time, between baseline and post treatment scan (62).

3.2.d. The effects of rTMS on brain activity and negative symptoms of

schizophrenia—Dlabac-de Lange and colleagues examined whether 3 weeks of 10 Hz rTMS, applied to the bilateral DLPFC, would improve frontal brain activation in patients with negative symptoms of schizophrenia. The active treatment group showed increased activity in the right DLPFC and the right medial frontal gyrus and decreased activity in the left posterior cingulate. Although there was a significant improvement in SANS with active treatment, there was no correlation with imaging results (63).

3.2.e. Summary: functional brain changes associated with rTMS—The rTMS literature suffers from the same diversity of patient samples and technical details as the APM literature reviewed above. In addition, rTMS studies differ from one another in the brain region stimulated. Nonetheless, we note that four of five studies reported functional activity changes after rTMS. Of these, 3 studies reported functional activity changes in the normalization direction in frontal regions including MFG (59, 63), IFG (59, 60), cingulate gyrus (60, 63), precentral gyrus (59) and DLPFC (63) even though the location of brain stimulation differed in each case and was in the temporo-parietal cortex in two of the papers. Taking all of the studies together, we note a continuation of the same pattern as in APM studies, that findings are scattered across brain regions in various studies but there is an over-representation of frontal regions whose activity have changed with treatment.

3.3. Functional brain changes associated with tDCS

Mondino and colleagues assessed the effects of tDCS on seed-based FC of the left TPJ in patients suffering from treatment-resistant AVH (75). Following active tDCS when compared to sham tDCS, left TPJ resting state FC was reduced with the right IFG and left anterior insula but increased with the left DLPFC, precuneus and left angular gyrus. The active tDCS group showed a significant improvement in AVH and negative symptom severity and the reduction in AVH severity was correlated with FC reduction between the left TPJ and the left anterior insula. This tDCS study once again highlights the role of frontal regions in response even though treatment was focused on the TPJ.

Palm and colleagues conducted a proof –of-concept study to examine the effects of tDCS of the PFC, added to stable APM, on seed based FC of the bilateral DLPFC and subgenual area in patients with predominantly negative symptoms (41). Sixteen patients were randomized to 10 sessions of active or sham tDCS and underwent 4 fMRI scans immediately before and after the 1st and 10th tDCS. Compared to sham treatment, the active tDCS group showed significant increases in resting state FC between left DLPFC and left inferior/middle temporal gyrus; right DLPFC and right insula, right IFG, left claustrum; and between the right subgenual gyrus and right thalamus. Although, there was a significant improvement in SANS and PANSS scores, there was no correlation between the FC changes and clinical outcome measures.

3.3.a. Summary: functional brain changes associated with tDCS—In both of the studies, the effects of tDCS were assessed on seed based FC changes during resting state. In one of the studies left TPJ FC was reduced with the right IFG and left anterior insula but increased with the left DLPFC, precuneus and left angular gyrus (75). The other study

examined FC changes with DLPFC and subgenual gyrus seeds and reported FC changes mainly in temporal and subcortical regions (41),

3.4. Functional brain changes associated with CRT

3.4.a. The effects of CRT on brain activation during tasks of working memory

—We identified five studies in this group. Three of these used N-back tasks to assess WM (64-66), one used an N-back task and a lexical task together (67), and another used a verbal memory task (68).

Wykes and colleagues examined brain activity following CRT (64). Twelve male patients receiving CRT (n=6) or control therapy (n=6) and 6 healthy males were included in the study. Nine patients were on FGA and three were on SGA treatment. CRT consisted of “pen-and-paper” exercises to ameliorate cognitive flexibility, working memory, and planning. After 12 weeks of treatment, investigators found an increase in right IFG and bilateral occipital activation during a visual N-back task. There were no changes in symptoms or disability.

Bor and colleagues explored the effect of CRT within spatial and verbal WM regions (65). Patients (stable on APM) received CRT training multiple cognitive domains or no additional treatment. After CRT, investigators detected over-activations in left inferior/middle frontal gyrus, left cingulate gyrus and left IPL during a spatial working memory task. Improvements in attention/vigilance and reasoning/problem solving cognitive tasks was associated with over-activation within the left VLPFC, left ACC and left parietal areas.

Subramaniam and colleagues investigated the impact of intensive computerized CRT on WM. After treatment (at 16 weeks), the active training group showed increased activation in left MFG and improved their 2-back working memory performance and these two changes correlated with one another. Improvement on the N-back and bilateral MFG signal after 16 weeks was associated with better occupational functioning assessed at 6 month follow up (66).

Haut and colleagues evaluated the effects of either CRT or cognitive behavioral social skills training (CBSST) (67). After treatment, CRT group showed significant increases in frontopolar cortex, DLPFC, and anterior cingulate gyrus activation (greater than CBSST or healthy controls) during verbal and visual working memory tasks. Enhanced left frontopolar cortex and left DLPFC activation was significantly correlated with working memory performance.

Finally, Wexler and colleagues reported on the effects of repetitive, progressively more difficult exercises on verbal working memory. The purpose of the study was to evaluate training-related changes in verbal memory and its association with changes in inferior frontal cortex activation. They reported that patients who showed improvement in verbal memory also showed increased task-related activation in the left inferior frontal cortex (68).

3.4.b. The effects of CRT on functional connectivity during a working memory task

—Pénades and colleagues conducted a controlled, randomized study and investigated

structural and functional connectivity brain changes in a relatively larger patient cohort (stable treatment with SGA) who received CRT or social skills training (SST) and in healthy controls. After CRT, patients showed decreased activation in the central executive network (CEN) in regions that had shown overactivation at baseline (i.e. towards normalization) as well as in some DMN regions. The reduction of overactivation in CEN correlated with improvements in total cognition scores (42)

3.4.c. The effects of CRT on brain activation during tasks of emotion

recognition—Hooker and colleagues published two papers reporting functional changes following CRT, consisting of both auditory-based cognitive training (AT) and social cognitive training (SCT), in patients with schizophrenia. Following joint AT/SCT training, they reported a greater increase in right postcentral gyrus activity during recognition of both positive and negative emotions as well as more behavioral improvement in emotion perception as compared with a computer-game control group. The increase in right postcentral gyrus activity predicted behavioral improvement in emotion processing among all participants. Against the authors' expectation, an intervention-related decrease was found in gyrus rectus and medial superior frontal gyrus in CRT group compared to CG (during recognition of negative emotions). There were no significant intervention related improvements in functional outcome or general cognition (69). The other study investigated the intervention-related neural activity changes in emotion processing regions, particularly in amygdala, during correct identification of the six basic emotional expressions (happy, surprise, fear, angry, disgust, and sad) in the same subjects. Patients in the CRT group improved in perceiving emotions and showed increased neural activity included bilateral amygdala, right putamen and right medial PFC during emotion recognition (70).

3.4.d. The effects of CRT on brain activation during a reality monitoring task—

Subramaniam and colleagues investigated the impact of CRT on medial PFC activity during a reality monitoring task. Social functioning was also assessed 6 months after the training. The CRT group indeed exhibited increased medial PFC activity during the reality monitoring task after the intervention and this was correlated with the behavioral improvement in reality monitoring and verbal memory. Further, the activation change in mPFC at 16 weeks was significantly correlated with better social functioning at 6 months (71).

3.4.e. The effects of CRT on brain activation during a verbal fluency task—

Vianin and colleagues investigated the effect of 14 weeks of CRT (involving problem-solving and verbal mediation techniques) in patients on stable doses of SGA and examined brain changes during a verbal fluency task. The CRT group showed an activation increase in L IFG, R IPL, R precentral gyrus, L middle occipital cortex, L middle cingulate cortex and L SPL after treatment. The CRT group also showed a better post treatment performance in the Color-Word Stroop Test and in the Matrix Reasoning Test (72).

3.4.f. Summary: functional brain changes associated with CRT—

We identified nine studies examining functional activity changes following CRT and all nine reported frontal functional activity changes following CRT. This was an impressive finding because

the content of CRT interventions vary widely, conceptually similar to APM and rTMS interventions. One study reported activity decreases following CRT in gyrus rectus and medial superior frontal gyrus (69) against the authors' predictions. The intervention arm in that study did not show any changes in cognition or functioning, raising the question of whether the intervention was delivered as intended. The remaining studies reported activity increases in frontal areas. Five studies reported activity increase in IFG (64-66, 68, 72), 3 studies reported in PFC (67, 70, 71) and 3 reported changes in cingulate gyrus (65, 67, 72). Other frontal regions, which showed activity increase, were: MFG (65, 66), precentral gyrus (69, 72), DLPFC and frontopolar cortex (67), VLPFC (65) and SMA (72).

One study investigated FC changes in CEN and DMN after CRT and reported a decrease in connectivity of frontal and parietal CEN regions and of DMN regions (42). These changes were normalizations of abnormally elevated FC findings.

Consistent with the pattern from previously-reviewed modalities, we also see scattered changes reported in multiple other brain regions, but none with the consistency of changes in frontal regions.

3.5. Functional brain changes associated with CBTp

3.5.a. The effects of CBTp on brain activation during tasks of emotion

processing—Kumari and colleagues evaluated brain changes following CBTp during an affect processing task. The purpose of the study was to investigate whether schizophrenia patients with positive symptoms would display an activity decrease following CBTp, within the network of brain regions processing facial expressions, particularly those related to threat (i.e. fearful and angry expressions). After CBTp patients showed a reduction in all PANSS subscale scores. Post-treatment fMRI revealed decreased brain activity in inferior frontal, insula, thalamus, putamen and occipital areas during the processing of fearful and angry expressions compared to baseline in the CBTp group (73).

3.5.b. The effects of CBTp on functional connectivity during tasks of emotion

processing—Recently, Mason and colleagues investigated FC alterations in facial affect processing areas after CBTp. Investigators hypothesized that patients would show reduction of affective and salience region influence after CBTp. FC was assessed from left amygdala and right DLPFC seeds by means of the psycho-physiological interaction (PPI) approach. Greater increases in amygdala connectivity with right DLPFC, right IPL, right posterior cingulate gyrus, left SPL, left postcentral gyrus and left thalamus were indeed observed in CBTp group. Additionally, greater increases in DLPFC connectivity with dorsal and subgenual portions of the left ACC and with left posterior cingulate were observed compared to ST (74).

3.5.c. Summary: functional brain changes associated with CBTp—In both of the CBTp studies functional changes were assessed during facial affect processing. In one of the CBTp studies, functional activation was reduced in IFG, insula, putamen, thalamus and occipital areas (73). The other study assessed FC changes with amygdala and DLPFC seeds and reported FC changes mainly in frontal and parietal regions (74).

4. DISCUSSION

In the present review, we examined fMRI-based outcome measures in treatment studies of schizophrenia. The treatment modalities included APM, rTMS, CRT, CBTp and tDCS. Taking the findings of our systematic review together, we have found that the most consistent finding across studies is the normalization of functional activity in frontal cortical regions. For example, eight out of nine brain activation studies and six out of eight FC studies identified this pattern in APM studies. Likewise, four out of five rTMS studies found normalization of frontal activity, as did both tDCS, all nine CRT, and both CBTp studies. Where control data were available, the change in frontal regions with antipsychotic therapy was in the direction of normalization; where such comparisons were not available, the change observed with antipsychotic therapy was always an increase in brain activation or FC. These findings provide strong evidence that the various schizophrenia treatment modalities share modulation of frontal cortex function as a key mechanism.

The patterns we observed had two additional features: first, findings emerged across many parts of frontal cortex, including frontal pole, orbitofrontal cortex, medial PFC, DLPFC, anterior cingulate cortex, and SMA. Second, the frontal findings were often accompanied by findings in a network of other brain regions but these other regions varied from study to study. Taken together, these findings suggest that treatments for schizophrenia share the feature of normalizing brain activity in distributed circuits which share frontal cortical hubs as their common feature. Additional details of the fMRI findings in each study are likely determined by their technical and clinical features.

This literature is diverse, with many different kinds of study designs, patient characteristics, follow up durations, and imaging approaches utilized. Given this diversity, it is not surprising that many findings do not replicate across studies. The literature we reviewed is sizable when taken together but the number of papers is small for any single modality. Therefore, the relatively small body of evidence for each modality likely contributes to the variability we observe. There is another source of systematic variability: the different fMRI approaches. Brain activation studies identify change in brain activity in response to specific challenges. In our review, such challenges included both cognitive and emotional processing tasks. It is unlikely that these tasks would activate identical circuits, but certain elements such as executive function may be shared, leading to similar activation changes in frontal areas. In contrast to brain activation studies, FC studies examine similarity of signal timecourses in pairs of brain areas. These can be during rest, or in the context of task performance (e.g. psychophysiological interaction or PPI studies). FC in general provides a very different kind of insight when compared with brain activation, and the insights from rest and PPI studies are quite different from one another. These different study designs no doubt introduced great variability into our analysis, although we observe changes that are consistent with normalization of activity in schizophrenia as described above.

A substantial body of evidence suggests that frontal lobe abnormalities are involved in the neurobiology of schizophrenia, especially in the negative and cognitive symptoms of the illness (76). Together with early studies which have found dysmorphology in frontal structures (77-79), neuropsychological studies also provided clear support for frontal lobe

dysfunction in patients with schizophrenia (80-84). In addition to these findings, functional neuroimaging studies using PET (85-87), SPECT and fMRI (88, 89) have revealed evidence regarding the involvement of prefrontal dysfunction in schizophrenia. But the relationship between these findings and clinical features is not well-understood (90). Neurophysiological abnormalities in frontal cortex have been found in high-risk subjects and in patients with first episode psychosis (91). Broadly speaking, our review adds to this large literature by indicating that treatments for schizophrenia normalize functional activity in the frontal cortex.

What cellular/molecular changes may underlie the circuit-level changes we observe? All APMs in our review are dopamine D2 receptor antagonists, suggesting that dopamine blockade may play a role. However, rTMS and tDCS do not directly modulate dopamine systems and instead are believed to work through glutamate and GABA modulation (92, 93). There is no clear evidence on which mechanisms are involved in CRT or CBTp but to the extent that these therapies alter cortical information processing they would also be expected to modulate glutamate and GABA systems. Using magnetic resonance spectroscopy, we and others have shown abnormalities in both glutamate and GABA concentrations (94, 95), providing a potential substrate for the changes we observe with treatment. In summary, we do not have definitive evidence for the involvement of any single neurotransmitter system but it appears likely that multiple treatment modalities converge on glutamate and GABA systems that control cortical information processing.

Another significant observation that emerges from our review is that nonpharmacological treatments such as rTMS and CRT modulate the same frontal regions as APMs, even when the targeted brain region is outside the frontal cortex, as in the case of some rTMS studies. This provides additional support for the importance of frontal modulation in the treatment of schizophrenia. There are several limitations to the current review arising from the characteristics of the existing literature. Firstly, the number of included studies, especially using tDCS, CBTp, rTMS, is limited. Most studies we reviewed used APMs. The results of the studies were presented in different categories such as within group pre- and post-treatment or between groups with treatment/placebo. In most of these studies, only PFC regions were examined and in task-based studies tasks that are designed to elicit activation in prefrontal regions were used. The sample size of most studies is small. No power analysis was reported in any study and patient characteristics such as subtype, resistance to treatment, age of onset, baseline medication status and treatment durations differed greatly from each other. Long-term effects of treatments have not been explored in depth and due to short duration of follow up, studies do not provide information whether the potential normalization of functional activity in frontal regions persists over time. Most of the APM studies did not have a placebo group because of ethical considerations so one may not attribute functional changes to medication effects, rather than time. Furthermore, for studies which enrolled first episode patients, it was not possible to compare the intervention effects with a placebo so we are not able to distinguish treatment effects from functional changes related to clinical recovery or from the natural course of the disorder.

Secondly, the design of the rTMS studies we examined was quite specialized: investigators typically measured the focal functional alterations at or FC of the region to which the

stimulation was applied; therefore activity patterns in other cortical regions were not assessed. Thirdly, a number of the included studies did not examine the relationship between fMRI changes and clinical improvement or did so with a specific clinical finding (e.g. emotion perception). In addition, a number of investigations reported correlations between neural activity changes and behavioral performance improvement in particular tasks but did not report associations with symptom severity or daily/occupational functioning. Therefore, we cannot state that the functional changes we identify were correlated with clinical improvements. Furthermore, certain functional brain changes, for instance in the basal ganglia, may be related to off-target effects such as extrapyramidal effects of APMs (27). Finally, the majority of studies used tasks which engage frontal areas. Given that many studies do not provide information about the whole brain, nor employ comparison tasks designed to elicit activation in non-prefrontal regions, we cannot determine the specificity of treatment effects on PFC.

In conclusion, we have reviewed a large and diverse literature on schizophrenia treatments and found that all treatments regardless of modality modulate networks that include frontal brain regions. Although we were able to draw some conclusions from the literature, there is much room for improvement. Future studies should include whole brain analyses, or carefully-selected comparator regions that would not be expected to mediate treatment effects. Additionally, determining the impact of different treatment modalities with task-independent functional imaging methods and examining the relationship with clinical improvement may offer new insights into what features of cortical network modulation lead to effective treatments.

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Figure 1.
Detailed description of the literature search and study selection.

Table 1

Longitudinal fMRI studies of antipsychotic medications (Ns reflect those included in imaging analyses).

Study	Participants	Treatment		Treatment duration	MRIField Strength	Task(s)	Main Findings				Strengths/Limitations	
		Active	Control				Frontal	Temporal	Parietal	Occipital		Subcortical
The effects of APM on resting state functional connectivity												
Lui et al. (2010)	34 SZ (ANS) age: 24.6 (8.5)y ID: 7.8 (12.4) mo; 34 HC age: 25.0 (8.0)y	APM-free→ SGA (6 different APM)	N/A	6 weeks	3 T	Rest	↑ ALFF in: -R MFG ^a -L SFG ^a -R IFG ^a -B medial frontal g. ^a ↓ FC associated with: -R MFG -R IFG -B medial frontal g.	↑ ALFF in: -L STG ^a ↓ FC associated with: -L STG	↑ ALFF in: -R IPL ^a -L SPL ^a ↓ FC associated with: -R IPL	-	↑ ALFF in: -R caudate ^a ↓ FC associated with: -R caudate	<i>Strengths:</i> -Relatively large sample size -Confounding effects of chronic illness and prior treatment minimized by studying FES <i>Limitations:</i> -Treatment consisted of different SGA's with diverse mechanisms of action
Hadley et al. (2014)	21 SZ (6 ANS) age: 36.0 (10.2)y ID: 13.3 (9.5)y; 21 HC age: 35.5 (10.4)y	APM-free→risperidone	N/A	1 week	3 T	Rest	-	-	-	-	↑ FC between VTA/midbrain seed and B thalamus	<i>Limitations:</i> -Brief treatment duration (investigators aimed to elucidate the functional correlates of treatment-induced changes before clinical response is apparent) -fMRI sequence with relatively low spatial resolution -Only 6 FES patients -HC scanned only at baseline
Sarpal et al. (2015)	24 SZ (FES) ID: N/A; 24 HC (mean age was not given)	APM-free→ risperidone (N = 13)/ aripiprazole (N = 11)	N/A	12 weeks	3 T	Rest	↑ FC between: - R dorsal caudate seed and ACC ^a , R DLPFC ^a , R OFC ^a -R ventral rostral putamen seed and ACC ^a	↑ FC between: - R dorsal caudate seed and R anterior insula ^a	↓ FC between: -R ventral caudate/nucleus accumbens seed and B SPL and B supramarginal g. -L ventral caudate seed and R SPL	-	↑ FC between: -R ventral caudate/nucleus accumbens seed and L hippocampus ^a	<i>Strengths:</i> -Confounding effects of chronic illness and prior treatment minimized by studying FES. <i>Limitations:</i> -Analysis combined two SGA's with very different mechanisms of action; unable to perform drug-specific analysis due to limited power
Li et al. (2016)	20 FES (ANS) age: 22.9 (8.5)y ID: 6.4 (13.6)	APM-free→ SGA	N/A	1 year	3 T	Rest	↑ ALFF in: -R OFC	↑ ALFF in: -R IPL ↑ FC between: -B IPLs	↑ ALFF in: -R IPL	↓ ALFF in: -R occipital gyrus		<i>Limitations:</i> -Treatment consisted of different SGA's with diverse mechanisms of action (the details of SGA were not presented)

Study	Participants	Treatment		Treatment duration	MRIField Strength	Task(s)	Main Findings				Strengths/Limitations	
		Active	Control				Frontal	Temporal	Parietal	Occipital		Subcortical
	mo 16 HC age: 22.4 (4.4)y											<i>Strengths:</i> -Confounding effects of chronic illness and prior treatment minimized by studying FES -Long term treatment duration <i>Strengths:</i> -Increase of the signal to noise ratio by excluding datasets with EPI signal dropout in the seed region -Usage of rigorous preprocessing and motion “scrubbing” of scans <i>Strengths:</i> -Usage of rigorous preprocessing and motion “scrubbing” of scans
Kraguljac et al. (2016b)	22 SZ (17 ANS) age: 32.38 (10.43)y ID: 9.59 (9.94) y 19 HC age: 32.00 (9.02)y	APM-free→risperidone	N/A	6 weeks	3 T	Rest	↑ FC between: -medial PFC/ACC ^a	↓ FC between: -L auditory cortex ^a	↑ FC between: -Lingual gyrus ^a	↑ FC between: -Caudate ^a ↓ FC between: -R caudate ^a		
Kraguljac et al. (2016a)	22 SZ age: 32.38 (10.43)y ID: 9.59 (9.94) y 19 HC age: 32.00 (9.02)y	APM-free→risperidone	N/A	6 weeks	3 T	Rest		↓ FC between: -B fusiform gyrus	↓ FC between: -B lingual gyrus -B calcarine sulcus	↓ FC between: -L cerebellum		
The effects of APM on default mode network (DMN) functional connectivity during a cognitive task												
Sambataro et al. (2010)	17 SZ; age: 24.8 (5.7)y ID: 44.1 (67) mo 19 HC age: 26.3 (6.9)y	APM-free→olanzapine	N/A	2 scans at 4 and 8 weeks of olanzapine treatment	3 T	N-back	-↑ DMN FC strength in VMPFC ^a in SZ at 8 weeks vs. 4 weeks.	N/A (Authors looked only at brain regions within DMN)	N/A (Authors looked only at brain regions within DMN)	N/A (Authors looked only at brain regions within DMN)		<i>Limitations:</i> -No APM-free scans (scans acquired 4 and 8 weeks after start of treatment)
The effects of APM on functional connectivity during a motor task												
Stephan et al. (2001)	6 SZ; age: 25.8 (4.4)y ID: N/A 6 HC age: 27.5 (8.4)y	APM-free→olanzapine	N/A	3 weeks	1.5 T	Finger tapping	↓ FC between: -L anterior cerebellar seed and nine PFC regions (strongest finding in L orbito-medial PFC, BA 11/25) -R anterior cerebellar seed and B PM cortex (BA 6), four PFC regions (BA 45, 8, 11, 9) ↑ FC between: -R anterior cerebellar seed and L lateral PFC (BA 9), L OFC (BA 11)	↓ FC between: -L anterior cerebellar seed and STG (BA 22) -R anterior cerebellar seed and medial temporal cortex (BA 27/28), L insula ↑ FC between: -R anterior cerebellar seed and L inferior temporal cortex	↓ FC between: -R anterior cerebellar seed and L lateral parietal cortex (BA 40) ↑ FC between: -R anterior cerebellar seed and R occipital and medial parietal cortex (BA 7/31)	↓ FC between: -L anterior cerebellar seed and B occipital and B occipital mediodorsal thalamus -R anterior cerebellar seed and L thalamus ↑ FC between: -R anterior cerebellar seed and L putamen		<i>Limitations:</i> -Small sample size -Heterogeneous medication status at baseline -Brief treatment duration -No clinical assessment of treatment response

Study	Participants		Treatment		Treatment duration	MRI/Field Strength	Task(s)	Main Findings				Strengths/Limitations	
	Active	Control	Frontal	Temporal				Parietal	Occipital	Subcortical			
The effects of APM on functional lateralization during a motor task													
Bertolino et al. (2004)	17 SZ; age: 26.1 (8.3)y ID: N/A 17 HC age: 26.1 (7.2)y	APM-free→ olanzapine	N/A	2 scans; after 4 and 8 weeks of treatment	3 T	Visually paced motor task	↑ activation at 8wks vs. 4wks in contralateral PSM (suggesting that some aspects of functional lateralization improve with clinical improvement)	N/A (Authors investigated only PSM and PM cortices, which are in frontal and parietal lobes)	(See frontal findings)	N/A (Authors investigated only PSM and PM cortices, which are in frontal and parietal lobes)	N/A (Authors investigated only PSM and PM cortices, which are in frontal and parietal lobes)	Limitations: -No APM-free scans (scans acquired 4 and 8 weeks after start of treatment) -Aim was to study specific hypotheses about functional lateralization involving specific brain areas (PSM and PM), thus limited scope in the context of the current review.	
The effects of APM on brain activation during tasks of emotion processing													
Blasi et al. (2009)	12 SZ; age: 28.2 (6.3)y ID: 81.1 (67.5)mo; 12 HC age: 27.0 (4.8)y	APM-free→ olanzapine	N/A	2 scans; after 4 and 8 weeks of treatment	3 T	Emotion (anger, fear) processing	↓ R VLPFC activity in SZ vs. HC at 4wks -Relative normalization of abnormally low R VLPFC activity at 8wks (↑ R VLPFC activity in SZ at 8wks vs. 4wks)	- (Authors applied more stringent significance threshold for areas outside L amygdala and R VLPFC a priori regions)	- (Authors applied more stringent significance threshold for areas outside L amygdala and VLPFC a priori regions)	- (Authors applied more stringent significance threshold for areas outside L amygdala and VLPFC a priori regions)	↑ L amygdala activity in SZ vs. HC at 4wks -Relative normalization of abnormally high L amygdala activity at 8wks (↓ L amygdala activity in SZ at 8wks vs. 4wks)	Limitations: -No APM-free scans (scans acquired 4 and 8 weeks after start of treatment) -Small sample size	
The effects of APM on brain activation during cognitive tasks													
Honey et al., 1999	20 SZ; 10 HC	FGA→ risperidone (N = 10) age: 37.6 (13.4)y ID: 12.6 (10.1)y	FGA→FGA (N = 10) age: 37.2 (8.1)y ID: 12.9 (6.6)y	6 weeks	1.5 T	Verbal WM	↓ R DLPFC activity -↑ SMA activity	-	↑ posterior parietal (precuneus) activity	-	-	Strengths: -Presence of a patient control group that stayed on FGA Limitations: -Participants were not randomly assigned to treatment groups -Patients who were switched to risperidone had higher psychopathology scores at baseline and after 6 weeks compared to patients who stayed on FGA -HC scanned only at baseline	

Study	Participants	Treatment		Treatment duration	MRI/Field Strength	Task(s)	Main Findings				Strengths/Limitations	
		Active	Control				Frontal	Temporal	Parietal	Occipital		Subcortical
Snitz et al. (2005)	11 SZ (FES, ANS) age: 23.0 (5.9)y ID: N/A; 16 HC age: 23.4 (4.9)y	APM-free→ SGA (risperidone, olanzapine, quetiapine) (naturalistic treatment)	N/A	4 weeks	3 T	Preparing to overcome prepotency	→ DLPFC and ACC activity in SZ vs. HC at baseline. -Decreased hypoactivation of ACC but not DLPFC in SZ 4wks after SGA	N/A	N/A	N/A	N/A	<i>Strengths:</i> -Confounding effects of chronic illness and prior treatment minimized by studying FES. <i>Limitations:</i> -Small sample size -Treatment consisted of different SGA's with diverse mechanisms of action
Meisenzahl et al. (2006)	12 SZ (9 ANS) age: 33.50 (9.39)y ID: N/A; 12 HC age: 33.58 (9.27)y	APM-free (2 days wash out period for 3 patients)→ quetiapine	N/A	12 weeks	1.5 T	Continuous performance Test	→ L VLPFC activity during 2-back condition	-	→ R precuneus g. activity during 2-back degraded condition	→ B lingual g. activity during 2-back degraded condition	-	<i>Limitations:</i> -Small sample size -Patients with heterogeneous medication histories (9 drug naïve, 2 had been on SGA, 1 had been on FGA)
Schlagenhauf et al. (2008)	10 SZ age: 34.6 (12.9)y ID: 7.6 (9.37) y; 10 HC age: 33.8 (12.5)y	FGA (haloperidol, flupenthixol, fluphenazine)→ olanzapine	N/A	2 scans; after 2 weeks of FGA treatment and 2 weeks after switching to olanzapine	1.5 T	N-back	→ DLPFC activity during attention (0-back) condition in olanzapine-treated vs. typical APM -No change in DLPFC activity during working memory (2-back) condition in olanzapine-treated vs. typical APM	N/A	N/A	N/A	N/A	<i>Limitations:</i> -Small sample size -No patient control group that remained on FGA - Patients with heterogeneous medication histories (treatment duration and different FGA's)
Keedy et al. (2009)	9 SZ (FES) ID: N/A; 9 HC (mean age was not given)	APM-free→ APM (risperidone (N = 6), ziprasidone (N = 1), haloperidol (N = 2))	N/A	4-6 weeks	3 T	Visually guided saccade	→ activity in visual attention and sensorimotor systems (i.e., B supplementary eye fields and L frontal eye fields) → activity in B VMPFC, L cingulate motor region, L DLPFC, and R presupplementary eye fields	→ activity in B STG, B anterior insula	→ activity in B intraparietal sulci and B supramarginal g.	→ activity in B cerebellum → activity in dorsal striatum, L caudate and B mediodorsal thalamus		<i>Strengths:</i> -Confounding effects of chronic illness and prior treatment minimized by studying FES. <i>Limitations:</i> -Small sample size -Treatment consisted of different APM with diverse mechanisms of action
van Veelen et al. (2011)	23 SZ (FES) age: 25.3 (4.6)y ID: 4.9 (4.3) mo; 33 HC age: 24.5 (4.7)Y	APM-free→SGA (n = 13 olanzapine, n = 3 quetiapine, n = 4 risperidone, n = 3 ziprasidone)	N/A	10 weeks	1.5 T	Modified Sternberg working-memory	-No significant in DLPFC activity pre- and post-treatment					<i>Strengths:</i> -Confounding effects of chronic illness and prior treatment minimized by studying FES. <i>Limitations:</i> -Treatment consisted of different SGA's with

Study	Participants		Treatment duration	MRI/Field Strength	Task(s)	Main Findings				Strengths/Limitations	
	Active	Control				Frontal	Temporal	Parietal	Occipital		Subcortical
Ikuta et al. (2014)	14 FEP age: 22.0 (5.70y) ID:N/A; 14 HC age: 22.4 (6.16)y	Limited APM exposure (mean 5.57 ± 7.87 days including n = 5 ANS) → SGA (risperidone, aripiprazole)	12 weeks	3 T	Multisource interference task (MSIT) to measure attentional control	-↓ activity in R SFG, R precentral g., R frontal pole in FEP at 12wks vs. baseline -↓ activity in L SFG and L frontal pole in FEP at 12wks vs. baseline	-	-↓ activity in R postcentral g. and L central opercular cortex in FEP at 12wks vs. baseline	-↑ activity in L lateral occipital cortex in FEP at 12wks vs. baseline	-At baseline, ↑ activity in R globus pallidus and B thalamus in FEP vs. HC -↓ activity in R globus pallidus ^a , B thalamus, B brainstem, B cerebellum in FEP at 12wks vs. baseline	diverse mechanisms of action -Only male participants included <i>Strengths:</i> -Confounding effects of chronic illness and prior treatment minimized by studying FEP. <i>Limitations:</i> -Small sample size -Baseline scan not APM- free -Only male participants included

^aDenotes findings that are correlated with clinical treatment response. ACC = anterior cingulate cortex; ALFF = amplitude of low frequency fluctuations; ANS= antipsychotic naïve schizophrenia; APM = antipsychotic medication; B = bilateral; BA = Brodmann area; DLPFC = dorsolateral prefrontal cortex; FC = functional connectivity; FEP = first episode psychosis; FES = first episode schizophrenia; FGA = first-generation antipsychotic medication; HC = healthy control participants; ID = illness duration, mean (SD); IFG = inferior frontal gyrus; IPL = inferior parietal lobule; L = left; MFG = middle frontal gyrus; mo = months; N/A = Not available; OFC = orbitofrontal cortex; PFC = prefrontal cortex; PSM = primary sensorimotor cortex; R = right;; SFG = superior frontal gyrus; SGA = second-generation antipsychotic medication; SMA = supplementary motor area; SPL = superior parietal lobule; STG = superior temporal gyrus; SZ = schizophrenia patients; VLPFC = ventrolateral prefrontal cortex; VMPPC = ventromedial prefrontal cortex; y = years.

Table 2

Longitudinal fMRI studies of rTMS (Ns reflect those included in imaging analyses).

Study	Participants	Treatment		Treatment duration	MRI/Field Strength	Task(s)	Main Findings				Strengths/Limitations	
		Active	Control				Frontal	Temporal	Parietal	Occipital	Subcortical	
The effects of rTMS on brain activity and auditory hallucinations												
Fitzgerald et al. (2007)	3 SZ (with AVH) age: 33.3 (8.7)y ID: N/A; 4 HC age: -	APM (clozapine, amisulpride) → APM + rTMS to the L temporo-parietal cortex	N/A	1 Hz, 10 rTMS sessions	3 T	Word generation	-↑ activity in L frontal - precentral cortex (L middle frontal gyrus, L precentral gyrus) -↓ activity in L IFG		-↑ activity in L temporo-parietal cortex (angular gyrus), L superior parietal gyrus, L inferior parietal gyrus)	-↓ activity in R middle occipital gyrus	Limitations: -Small sample size -HC scanned only at baseline -No patient control group	
Kindler et al. (2013)	30 SZ+ SADP with AVH) ID: N/A	APM → APM+ 1 Hz rTMS to the L temporo-parietal cortex (N = 7) age: 38.6 (11.4)y	1) rTMS treatment control group: APM → APM + Theta Burst Stim (N = 8) to the L temporo-parietal cortex age: 34.1 (8.0)y 2) Control treatment group with TAU: APM → APM (N = 15) age: 46.8 (13.5)y	1 Hz, 10 rTMS sessions/ TBS	3 T	Modified version of the language-processing	-↓ activity in L IFG and L cingulate gyrus	-↓ activity in L primary auditory cortex ^a			Strengths: -Relatively large sample size -Presence of a patient control group that stayed on APM Limitations: -No HC group	
The effects of rTMS on functional connectivity and auditory hallucinations												
Vercammen et al. (2010)	18 SZ (with AVH)	APM → APM + rTMS to the L temporo-parietal junction (N = 9) age: 38.88 (13.19)y	APM → APM + sham stimulation to the L temporo-parietal junction age: 33.67 (11.84)y	1 Hz, 12 rTMS sessions	3 T	Rest		↑ FC between: - L TPJ seed and R insula			Strengths: - Presence of a patient control group that received sham stimulation Limitations: -No HC group -ROIs were selected based on the	

Study	Participants	Treatment		Treatment duration	MRI/Field Strength	Task(s)	Main Findings				Strengths/Limitations
		Active	Control				Frontal	Temporal	Parietal	Occipital	
The effects of rTMS on brain activation during a working memory task											
Guse et al. (2013)	25 SZ age average (range): 36 (20-58)y ID: N/A 22 HC age average (range): 36 (20-58)y	APM → APM + rTMS to the L posterior middle frontal gyrus (N = 13) HC → rTMS	1)APM → APM + sham stimulation the L posterior middle frontal gyrus 2)HC / → sham stimulation	10 Hz, 15 rTMS sessions	3 T	N-back	- No significant working memory network	- in the common fronto- parietal and subcortical		<i>Strengths:</i> - Presence of a patient control group that received sham stimulation - Patients were centrally randomized to sham or real intervention group - Rater, investigators and patients were blind across all parts of the study.	investigators' previous study, in which they identified a relationship between AVH severity and FC between particular ROIs.
The effects of rTMS on brain activity and negative symptoms of schizophrenia											
Diabac-de Lange et al. (2015)	24 SZ age: 40.7 (12.6)y ID: 192 (127.8) mo	APM → APM + active rTMS to the bilateral DLPFC (N = 11) age: 40.7 (12.6)y ID: 192 (127.8) mo	APM → APM + sham stimulation to the bilateral DLPFC age: 30.8 (8.9)y ID: 90 (92.5)mo	10 Hz, 30 rTMS sessions	3 T	Tower of London (ToL) task	- ↑ activity in R DLPFC and R MFG - ↓ activity in L posterior cingulate			<i>Strengths:</i> - Presence of a patient control group that received sham stimulation <i>Limitations:</i> - Small sample size - No MRI based neuro-navigation to target DLPFC - The two groups differed significantly in age, duration of illness and PANSS General Psychopathology scores at baseline. (However the results were corrected for this difference in fMRI analyses).	

^aDenotes findings that are correlated with clinical treatment response. APM = antipsychotic medication; AVH = auditory verbal hallucinations; DLPFC = dorsolateral prefrontal cortex; FC = functional connectivity; HC = healthy control participants; ID = illness duration, mean (SD); IFG = inferior frontal gyrus; L = left; PFC = prefrontal cortex; R = right; SZ = schizophrenia patients; tDCS = transcranial direct current stimulation; TPJ = temporo-parietal junction; y = years.

Table 3

Longitudinal studies of tDCS (Ns reflect those included in imaging analyses).

Study	Participants	Treatment		Treatment duration	MRI/Field Strength	Task(s)	Main Findings					Strengths/Limitations
		Active	Control				Frontal	Temporal	Parietal	Occipital	Subcortical	
Mondino et al. (2016)	23 SZ	APM→ APM+ active tDCS (N = 11) age: 36.7 (9.7) y ID: 11.8 (3.3)y	APM→ APM+ sham tDCS (N = 12) age: 37.3 (9.7)y ID: 12.2 (1.9) y	10 sessions of active tDCS (2 mA, 20 min) or sham tDCS (2 sessions/day for 5 days)	1.5 T	Rest	↓ FC between: - L TPJ seed and R IFG ↑ FC between: - L TPJ seed and L insula ^a	↓ FC between: - L TPJ seed and L anterior insula ^a	↑ FC between: - L TPJ seed and precuneus and L angular gyrus			<i>Limitations:</i> -Small sample size -Investigators applied second fMRI session, 1 h after the end of the last tDCS session that may reflect the acute effect of tDCS instead of cumulative effect of 10 tDCS sessions. -Several parameters which may influence tDCS outcomes were not controlled (coffee intake, satiation-levels, quality and amount of sleep or exercise). -No HC group
Palm et al. (2016)	16 SZ ID: 10.5 (9.9) y	APM→ APM+ active tDCS of PFC (N = 8) age: 38.4 (12.9)y	APM→ APM+ sham tDCS of PFC (N = 8) age: 34.1 (10.7)y	10 sessions of active tDCS (2 mA, 20 min) or sham tDCS (anode: left DLPFC/ F3; cathode: right supraorbital/ F4) (2 weeks)	NA	Rest	↑ FC between: - R DLPFC seed and R IFG	↑ FC between: - L DLPFC seed and L inferior/middle temporal gyrus - R DLPFC seed and R insula		↑ FC between: - R DLPFC seed and L claustrum gyrus - R subgenual gyrus seed and R thalamus gyrus		<i>Limitations:</i> -Small sample size - Patients with heterogeneous medication histories - Imbalance in participants' gender and handedness -Presence of negative symptoms were defined according to clinical judgement <i>Strengths:</i> -Presence of a dual mode tDCS device which includes a novel sham mode that mimics sensory artefacts of tDCS -Presence of pre-evaluated tDCS conditions -No HC group

^a Denotes findings that are correlated with clinical treatment response. APM = antipsychotic medication; AVH = auditory verbal hallucinations; DLPFC = dorsolateral prefrontal cortex; FC = functional connectivity; HC = healthy control participants; ID = illness duration, mean (SD); IFG = inferior frontal gyrus; L = left; PFC = prefrontal cortex; R = right; SZ = schizophrenia patients; tDCS = transcranial direct current stimulation; TPJ = temporo-parietal junction; y = years.

Table 4

Longitudinal fMRI studies of cognitive remediation therapy (N's reflect those included in imaging analyses).

Study	Participants	Treatment		Control	Treatment duration	MRIField Strength	Task(s)	Main Findings				Strengths/Limitations	
		Active						Frontal	Temporal	Parietal	Occipital		Subcortical
The effects of CRT on brain activation during tasks of working memory													
Wexler et al. (2000)	8 SZ average age (range):46 (35-54) y ID: N/A	APM→ APM + CRT	N/A		10 weeks (20-30 h)	1,5 T	Verbal memory	-↑ activity in L IFG ^a				<i>Limitations:</i> -Small sample size -No HC group -No patient control group	
Wykes et al. (2002)	12 SZ ID: N/A 6 HC mean age: 36 y	APM→APM + CRT (N = 6) mean age: 35 y	APM→APM + control therapy (consisted of occupational therapy activities) mean age: 36 y		12 weeks (40 h)	1,5 T	N-back	-↑ activity in R IFG		-↑ activity in B occipital (lingual gyrus)		<i>Strengths:</i> - Presence of a patient control group that received control therapy <i>Limitations:</i> -Small sample size - Patients had been very disabled than the typical clinical sample	
Haut et al. (2010)	18 SZ + SADP ID: N/A 9 HC age: 40.0 (6.0)y	APM→APM + CRT (N = 9) age: 36.4 89.2)y	APM→APM + SST age: 39.5 (7.7)y		4-6 weeks (25 h)	3 T	N-back lexical decision	-↑ activity in L dorsal PFC and L DLPFC ^a , anterior cingulate gyrus and L frontopolar cortex ^a and R frontopolar cortex ^a (during word WM task) -↑ activity in L frontopolar cortex ^a and R frontopolar cortex; R and L dorsal PFC and anterior cingulate gyrus (during picture WM task)	-↑ activity in insula (during picture WM task)			<i>Strengths:</i> - Presence of a patient control group that received control therapy	
Bor et al. (2011)	17 SZ; 15 HC age: 30.1 (7.5) y	APM (aripiprazole, amisulpride, olanzapine, risperidone)→ APM + CRT (N = 8) age: 30.5 (8.3)y ID: 5.4 (3.4) y	APM→APM + no intervention age: 28.5 (7.2)y ID: 5.9 (5.2)y		7-weeks (28 h) (3 months between two scans)	1,5 T	N-back	-↑ activity in L IFG, L MFG, L cingulate gyrus ^a , L VLPFC (Broca' s area) ^a (for spatial working memory)		-↑ activity in L IPL/ precuneus ^a (for spatial working memory)		<i>Strengths:</i> - Presence of a patient control group	
Subramaniam et al. (2014)	28 SZ ID: 19.4 y;	APM →APM + CRT (N = 15)	APM→APM + CG placebo		16 weeks (80 h)	3 T	N-back	-↑ activity in L MFG and R MFG ^a and L				<i>Strengths:</i> - Clinical symptoms,	

Study	Participants		Treatment		Treatment duration	MRIField Strength	Task(s)	Main Findings		Strengths/Limitations			
	Active	Control	Frontal	Temporal				Parietal	Occipital	Subcortical			
<i>The effects of CRT on functional connectivity during a working memory task</i>													
Penades et al. (2013)	13 HC age: 44.27 (11.2)y	age: 40.69 (12.7)y (no APM in 4 patients)→CRT	age: 41.21 (9.48)y	4 months (40 h)	3 T	N-back	↓ the central executive network (CEN) in regions: - B MFG ^a , B IFG ^a anterior cingulate ^a (overactivation in CEN during task related responses at baseline normalized after treatment toward the patterns observed in HC) Y in DMN activation in regions: - anterior cingulate, cingulate gyrus	↓ in DMN activation in regions: - L middle temporal gyrus	↓ the central executive network (CEN) in regions: -B IPL ^a , B SPL ^a and B precuneus ^a (overactivation in CEN during task related responses at baseline normalized after treatment toward the patterns observed in HC) Y in DMN activation in regions: - B precuneus, L supramarginal gyrus	↓ in DMN activation in regions: -B cuneus	<i>Strengths:</i> -Structural and diffusion tensor imaging were conducted in addition to fMRI - Relatively long treatment duration -Relatively large sample size <i>Limitations:</i> - Patients with heterogeneous medication profiles (different APM, some of the patients were polymedicated)	neuropsychological performances and occupational functioning were assessed at baseline, after the intervention, and at 6-month follow-up <i>Limitations:</i> - Patients with heterogeneous medication profiles (one or combination of APM, antidepressants, mood stabilizers, benzodiazepines, anticholinergic) - SZ had higher functioning than the typical clinical sample	
<i>The effects of CRT on brain activation during tasks of emotion recognition</i>													
Hooker et al. (2012)	22 SP	APM→ APM + CRT (ABCT + SCT) (N = 11) age: 51.2 (5.8)y ID: 28.0 (8.3) y	APM→APM + CG placebo age: 41.0 (8.4)y ID: 20.6 (11.6) y	10 weeks (50 h)	4 T	positive and negative facial emotion recognition	Compared to CG group: -↓ activity in gyrus rectus and medial superior frontal gyrus in negative emotions compared to object condition -↓ in precentral gyrus for positive (versus negative) emotions	Compared to CG group: -greater ↑ activity in R postcentral gyrus activity ^a during emotion recognition of both positive and negative emotions	↑ activity in ventral striatum for positive (versus negative) emotions		<i>Limitations:</i> -Small sample size -Participants were mostly male -Since the patients received both ABCT and SCT, it is not possible to distinguish the effects of those interventions -Social cognition training was only 5–15 min per day -Instead of face-processing conditions, objects were used at baseline to compare the non-emotional information between baseline and post treatment in the study -No HC group		

Study	Participants	Treatment		Treatment duration	MRIField Strength	Task(s)	Main Findings			Strengths/Limitations
		Active	Control				Frontal	Temporal	Parietal	
Hooker et al. (2013)	22 SZ age: 40 (1.17)y ID: 19.4 y 16 HC age: 45 (11.6)y	APM→ APM + CRT (ABCT + SCT) (N = 11) age: 51.2 (5.8)y ID: 28.0 (8.3) y	APM→APM + CG placebo age: 41.0 (8.4)y ID: 20.6 (11.6) y	10 weeks (50 h)	4 T	facial emotion recognition	-↑ activity in R medial PFC (during emotion recognition of happy, surprise and fear expressions)			-↑ activity in B amygdala (R amygdala ^d), R putamen (during emotion recognition of happy, surprise and fear expressions) <i>Limitations:</i> -Small sample size -Participants were mostly male -Since the patients received both ABCT and SCT, it is not possible to distinguish the effects of those interventions -Social cognition training was only 5–15 min per day - There was no group-by-time interaction for the emotion vs. neutral contrast, to examine whether improvement in emotion processing was partially due to a general improvement in face processing -No HC group
<i>The effects of CRT on brain activation during a reality monitoring task</i>										
Subramaniam et al. (2012)	29 SZ age: 40 (1.17)y ID: 19.4 y 16 HC age: 45 (11.6)y	APM→ APM + CRT(N = 15) no APM in 5 SZ/CRT	APM→APM + CG placebo	16 weeks (80 h)	3 T	reality monitoring	-↑ activity in medial PFC ^d			<i>Strengths:</i> - Patients also re -evaluated after 6 months regarding social functioning <i>Limitations:</i> - Patients with heterogeneous medication profiles (one or combination of APM, antidepressants, mood stabilizers, benzodiazepines, anticholinergic)
<i>The effects of CRT on brain activity during a verbal fluency task</i>										
Vianin et al. (2014)	16 SZ	APM→ APM + CRT (N = 8) age: 27.63 (8.2)y ID: 92.13 (68.4) mo	APM→APM (TAU) age: 30.50 (9.4)y ID: 95.75 (72.2) mo	14 weeks (28 h in a one-to-one approach and 14 h of exercises at home) (6 months between two scans)	3 T	verbal fluency	Compared to TAU: -↑ activity in R precentral gyrus, L IFG, L middle cingulate cortex Compared to baseline scan (prior to CRT): -↑ activity in R precentral gyrus, L SMA and L precentral lobule	Compared to TAU: -↑ activity in R IPL, L SPL Compared to baseline scan (prior to CRT): -↑ activity in L IPL, R angular gyrus, R supramarginal gyrus	Compared to TAU: -↑ activity in L middle occipital cortex Compared to baseline scan (prior to CRT): -↑ activity in R inferior occipital gyrus, L middle occipital gyrus	<i>Limitations:</i> -Small sample size -Participants were mostly male -No HC group

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^aDenotes findings that are correlated with clinical treatment response. ABCCT = auditory-based cognitive training; APM = antipsychotic medication; AVH = auditory verbal hallucinations; B = bilateral; CEN = central executive network; CG = computer games CRT = cognitive remediation therapy; DLPFC = dorsolateral prefrontal cortex; FC = functional connectivity; HC = healthy control participants; ID = illness duration, mean (SD); IFG = inferior frontal gyrus; IPL = inferior parietal lobule; L = left; mo = months; R = right; SADP = schizoaffective disorder patients; SCT = social cognition training; SMA = supplementary motor area; SPL = superior parietal lobule; SST = social skills training; SZ = schizophrenia patients; TAU = treatment as usual; WM = working memory; VLPFC = ventrolateral prefrontal cortex; y = years.

Table 5

Longitudinal fMRI studies of CBTp (Ns reflect those included in imaging analyses).

Study	Participants	Treatment		Treatment duration	MRIField Strength	Task(s)	Main Findings				Strengths/Limitations	
		Active	Control				Frontal	Temporal	Parietal	Occipital		Subcortical
The effects of CBTp on brain activation during tasks of emotion processing												
Kumari et al. (2011)	38 SZ	APM→APM + CBTp (N = 22) age: 35.68 (7.82)y ID: 10.91 (7.70) y	APM→APM TAU age: 39.19 (9.37) y ID: 13.37 (10.16) y	6-8 months	1.5 T	affect processing	↓ activity in B IFG ^a (during fearful and angry expressions)	↓ activity in R insula ^a (during fearful and angry expressions)		↓ activity in L occipital areas ^a (during fearful and angry expressions)	↓ activity in B putamen ^a , L thalamus ^a (during fearful and angry expressions)	Strengths: -The therapists were supervised by one of the two investigators who have extensive experience of CBTp Limitations: -Participants were not assigned randomly into treatment groups -Anxiety level, which is known to be critical in threat perception and paranoia levels, was not measured. -No HC group
The effects of CBTp on functional connectivity during tasks of emotion processing												
Mason et al. (2015)	38 SZ; 20 HC age: 37.3 (12.5)y	APM→APM + CBTp (N = 22) age: 35.7 (7.82)y ID: 10.9 (7.70)y	APM→APM age: 39.2 (9.37)y ID: 13.4 (10.2) y	6-8 months	1.5 T	implicit facial affect processing	Compared to standard treatment: ↑ FC between: -amygdala seed and R DLPFC, R posterior cingulate gyrus ↓ FC between: - amygdala seed and L IFG ↑ FC between: -DLPFC seed and L ACC, L posterior cingulate	↓ FC between: - amygdala seed and L insula	Compared to standard treatment: ↑ FC between: -amygdala seed and R IPL ^a , L SPL, L postcentral gyrus	Compared to standard treatment: ↑ FC between: -amygdala seed L thalamus	Limitations: -Participants were not assigned randomly into treatment groups - Healthy controls were tested on a single occasion	

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Denotes findings that are correlated with clinical treatment response. ACC = anterior cingulate cortex; APM = antipsychotic medication; CBTp = cognitive behavior therapy for psychosis; DLPFC = dorsolateral prefrontal cortex; FC = functional connectivity; HC = healthy control participants; ID = illness duration, mean (SD); IFG = inferior frontal gyrus; IPL = inferior parietal lobule; L = left; R = right; SZ = schizophrenia patients; SPL = superior parietal lobule; y = years.