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# Neural Effects of Cognitive Training in Schizophrenia: A Systematic Review and Activation Likelihood Estimation Meta-analysis

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## ABSTRACT

**BACKGROUND:** Cognitive dysfunction is a core feature of schizophrenia and a strong predictor of functional outcome. There is growing evidence for the effectiveness of behaviorally based cognitive training programs, although the neural basis of these benefits is unclear. To address this, we reviewed all published studies that have used neuroimaging to measure neural changes following cognitive training in schizophrenia to identify brain regions most consistently affected.

**METHODS:** We searched PubMed for all neuroimaging studies examining cognitive training in schizophrenia published until December 2018. An activation likelihood estimation meta-analysis was conducted on a subset of functional magnetic resonance imaging studies to examine whether any brain regions showed consistent effects across studies.

**RESULTS:** In total, 31 original neuroimaging studies of cognitive training were retrieved. Of these studies, 16 were functional neuroimaging studies, and 15 of these studies reported increased neural activation following cognitive training, with increased left prefrontal activation being the most frequently observed finding. However, activation likelihood estimation meta-analysis did not reveal any specific brain regions showing consistent effects across studies but rather suggested a broader, more distributed pattern of effects resulting from the interventions tested.

**CONCLUSIONS:** Although several studies reported increased left prefrontal cortical activation after cognitive training, the lack of statistically significant overlap of brain regions affected by training across studies suggests broad effects of training on brain activation, possibly due to the variety of training programs used.


*Keywords:* Cognitive remediation therapy, Meta-analysis, Neuroimaging, Neuroplasticity, Prefrontal, Psychosis

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Cognitive dysfunction is a core feature of schizophrenia and is a strong predictor of employment, relationships, and independent living (1). Cognitive deficits include problems with short-term memory, attention and reasoning, and social cognitive abilities such as recognizing facial displays of emotion (2,3). To date, efforts to target these deficits pharmacologically have been largely ineffective (4). For example, large clinical trials of second-generation antipsychotics show only modest improvements in cognitive function (5), as have studies of adjunctive pharmacotherapy for cognitive deficits (6), while studies of novel therapies that directly target cognition have been largely negative or inconclusive (7). These difficulties in targeting cognition reflect the wider difficulties in psychiatric drug discovery that have been commented on elsewhere (8,9).

In this context, behaviorally based cognitive training (CT) approaches have become a substantial research focus. CT (or cognitive remediation therapy) seeks to improve cognitive processes (e.g., in attention, memory, executive function, and social cognition) using a combination of strategy, drill, and practice so as to lead to durable benefits in terms of functional outcomes (10). These training programs may be administered via pen and paper or through specialized computer software on a regular basis and over a period of weeks. In schizophrenia, a meta-analysis in more than 2000 individuals found a moderate effect size for improvements in cognition following CT ($d$ = 0.45) (11).

A key aim for CT is to advance our understanding of the neural mechanisms underlying therapeutic action. This is important in order to better understand how CT affects cognitive function (i.e., what brain areas and cognitive systems are most sensitive to the effects of CT?). This can also provide more evidence that particular CT programs are effective by showing that they have an impact that can be observed at the level of brain as well as behavior. Better understanding of the neural mechanisms underlying CT may also help to inform future studies that seek to combine CT with other brain-based interventions (e.g., pharmacological interventions) or repetitive

 

transcranial magnetic stimulation, which can be applied to different regions of the cerebral cortex and may enhance neuronal plasticity (12).

In a meta-analysis of nine studies that had investigated the neural correlates of CT, Ramsay and MacDonald (13) reported what they described as "preliminary" evidence of increased activation in the lateral and medial prefrontal cortex (PFC), parietal cortex, insula, caudate, and thalamus following CT programs that were based on a variety of approaches. Since then, many new CT studies that included neuroimaging have been reported. In addition, the meta-analytic approach taken in the Ramsay and MacDonald (13) study and in a similar study by Wei *et al.* (14), known as activation likelihood estimation (ALE), has since been revised based on evidence that previous approaches yielded an inflated rate of statistically significant regional activations across studies (15). Given the substantially increased number of magnetic resonance imaging (MRI) studies of CT in schizophrenia now reported, and the limitations of previous meta-analytic strategies, the purpose of the current study was to undertake a systematic review and meta-analysis of all CT studies in schizophrenia that have included neuroimaging so far to examine neural changes following treatment in light of additional recently published studies and updated meta-analysis software.

## METHODS AND MATERIALS

We undertook a systematic search of PubMed for relevant original neuroimaging studies examining the effects of a CT program in patients with schizophrenia. This search, which included all articles published before December 2018, was based on the following search terms: "(cognitive remediation OR cognitive training) AND (schizophrenia OR schiz*) AND (MRI OR fMRI OR SPECT OR PET OR cortical thickness OR VBM OR DTI)," where fMRI indicated functional MRI, SPECT indicated single photon emission computed tomography, PET indicated positron emission tomography, VBM indicated voxel-based morphometry, and DTI indicated diffusion tensor imaging. This led to the identification of 182 studies in total, of which 27 were original studies that matched study criteria. This literature search was supplemented with a review of the references from each of the articles identified, highlighting a further four studies meeting study criteria, meaning that a total of 31 studies were included in our review. Figure 1 lists the number of studies included and excluded in this review as well as the reasons for inclusion and exclusion. Although we performed a systematic search of PubMed with a broad search term, it should be noted that there may be other relevant studies that were not identified by this specific search strategy.

Next, we used the ALE method in GingerALE 2.3.6 (15–19) to perform a meta-analysis to examine whether there were any brain regions affected by CT in schizophrenia that showed a statistically significant overlap across multiple studies. We used the latest version of GingerALE, which corrects an error in the correction for multiple comparisons that resulted in inflated $p$ values in previous versions (15).

We limited this meta-analysis to studies examining changes in task-evoked blood oxygen level–dependent (BOLD) response to ensure that only studies using the same method were compared ($n$ = 14 with findings reported in Montreal Neurological Institute [MNI] or Talairach coordinates). Single photon emission computed tomography studies ($n$ = 4) and studies including volumetric measures ($n$ = 5), measures of cortical surface area ($n$ = 1), diffusion tensor imaging ($n$ = 2), cortical thickness ($n$ = 2), and functional connectivity ($n$ = 6) were too few to be included in separate ALE meta-analyses (20).

Thus, our meta-analysis included coordinates from each of the clusters where either 1) patients with schizophrenia showed altered task-evoked BOLD response after a training period relative to before ($n$ = 7) or 2) patients with schizophrenia showed altered task-evoked BOLD response after a training period relative to before relative to changes observed in control treatment groups after the same period ($n$ = 7).

Where coordinates were presented in Talairach space, these were converted to MNI space using GingerALE ["Talairach to MNI (SPM)" transform] to input into the meta-analysis. Table 1 summarizes the main outcomes from the studies included in both our systematic review and our ALE meta-analysis ($n$ = 14). Table 2 summarizes the main outcomes from the studies included in our systematic review only ($n$ = 17). Supplemental Table S1 summarizes the main outcomes in more detail for all 31 studies included in our systematic review, including those also included in our ALE meta-analysis.

Maps of altered task-evoked BOLD response were created for each study by modeling individual coordinates as Gaussian functions. The width of each of these functions is calculated by GingerALE software based on each study's sample size; that is, GingerALE will model coordinates as wider Gaussian functions for loci from larger studies. Next, the overlap between these maps was used to calculate an ALE map. The probability of finding a particular value within an ALE map across studies was used to create a $p$-value image, which was thresholded at $p < .001$, uncorrected (cluster-forming threshold), and then cluster thresholded using 1000 threshold permutations and a cluster-level threshold of $p < .05$, family-wise error corrected.

Finally, we ran an a priori power analysis in G*Power 3.1.9.2 (21) to examine what sample size would be necessary to detect effects at least equal to those previously identified in the neuropsychological literature; for example, a meta-analysis of cognitive remediation therapy studies by Wykes *et al.* (11) identified a mean effect size of Cohen's $d$ = 0.45. Using a two-tailed dependent $t$ test, a total sample of 41 would be required to identify effect sizes of $d$ = 0.45 or greater with 80% power at $p$ = .05. Considering the fact that several neuroimaging methods require statistical thresholds to be corrected for multiple comparisons (e.g., fMRI), the true sample required is likely to be higher than 41.

## RESULTS

In total, 31 studies meeting search criteria were retrieved (see Figure 1). Studies carried out prior to 2005 were based on very small samples (i.e., $n \leq 6$ receiving the intervention), and only one of these studies (22) included a control group.

In terms of the cognitive remediation therapy approaches studied, nine studies specified their focus as being on executive function, with targeted training of executive

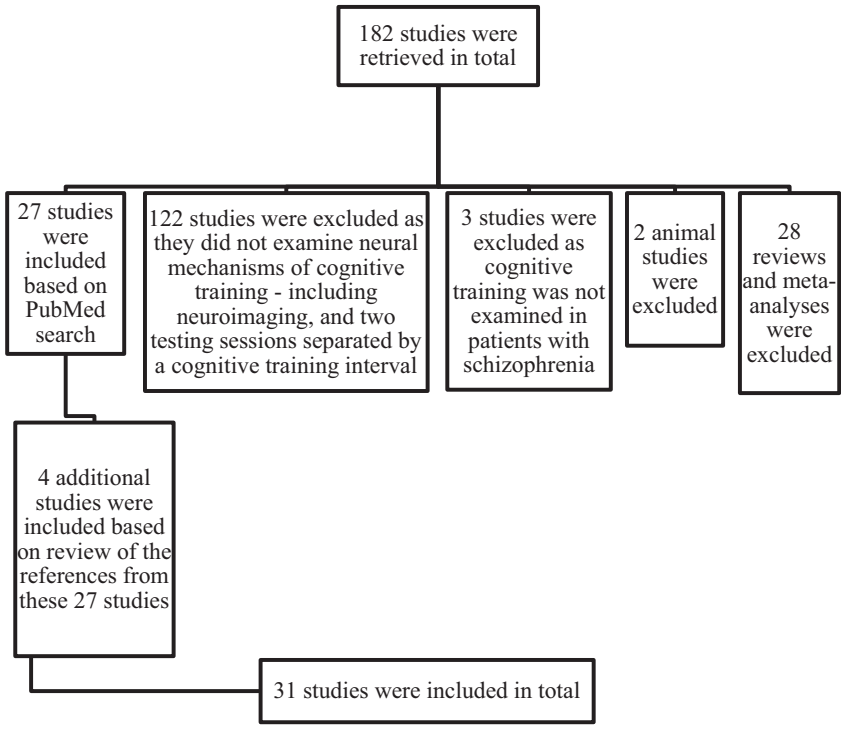


**Figure 1.** Flowchart of studies included and excluded from review.

subprocesses that included attention, working memory, planning, problem solving, logical thinking, and cognitive shift. An additional three studies examined effects of programs that focused on memory, including auditory verbal memory, relational memory, and semantic association memory; two studies examined only social cognition or social skills training; and 17 studies examined effects of programs that combined training in executive function, social cognition (including processes such as social perception and theory of mind), memory, and/or sensory processing (including visual and/or auditory processing).

The mean duration of the training interval for these studies was approximately 47.36 hours (based on 28 of the 31 studies that reported the training interval in minutes or hours) across a mean period of approximately 23.81 weeks. The training programs employed were reported to have been administered by a variety of means, including pen and paper, specialized computer software, and/or interactions with other individuals (e.g., in group sessions).

The mean sample size was 28.32 (SD = 15.66) across the 31 studies, with nine studies reporting sample sizes greater than 41, the sample size identified in our power analysis as the minimum required to identify effects similar to those reported in the neuropsychological literature (10,23–30).

Regarding the 14 studies included in the ALE analysis, five studies focused on executive function, two studies focused on memory (including relational memory and semantic memory), one study focused on social cognition, and six studies examined effects of programs that combined different cognitive processes. The mean duration of the training interval was approximately 43.77 hours (based on 13 of the 14 studies that reported training interval in minutes or hours) across a mean period of approximately 15.71 weeks. The mean sample size was 27.43 (SD = 8.45) across the 14 studies, with two studies included in the ALE meta-analysis reporting sample sizes greater than 41.

## Neuroimaging Findings

The most common finding across studies was increased prefrontal activation, indexed as either increased cerebral blood flow or increased BOLD response (16 studies—nine showing increased prefrontal activation in CT patients after training and seven showing increased prefrontal activation in CT patients after training relative to changes observed in control treatment groups). At the same time, however, changes in neural activation were also reported across a wide range of other brain areas following CT.

Specifically, the most common finding was of increased BOLD response in the left PFC (16 activation peaks reported in MNI or Talairach coordinates), including the cingulate, dorsal PFC, dorsolateral PFC, frontopolar cortex, inferior frontal gyrus, inferior frontal operculum, inferior/middle frontal gyrus, medial PFC, and middle frontal gyrus. The second most common finding was of increased BOLD response in the right PFC (nine peaks), including the dorsal PFC, dorsolateral PFC, frontopolar cortex, gyrus rectus/medial orbitofrontal cortex, inferior frontal gyrus, superior frontal gyrus, and superior frontal gyrus/media PFC.

Within the left parietal lobe (four peaks), increased BOLD response was reported in the left angular gyrus, left inferior

**Table 1. Functional Magnetic Resonance Imaging Studies of Cognitive Training in Schizophrenia Included in Systematic Review and Activation Likelihood Estimation Meta-analysis**

| First Author and Year (Reference) | *N* | Cognitive Process(es) Targeted | Weeks | Main Neural Activation Outcome(s) |
|---|---|---|---|---|
| Wykes, 2002 (22) | 18 | Executive function | 12 | Increased activation in PFC and other regions in CT patients after training |
| Haut, 2010 (32) | 27 | Executive function and memory | 4–6 | Increased activation in PFC and other regions in CT patients after training relative to other groups |
| Rowland, 2010 (43) | 34 | Relational memory | <1 | Altered activation across parietal, temporal and occipital lobes in CT patients after training |
| Edwards, 2010 (33) | 36 | Executive function | <1 | Altered activation in PFC and other regions in CT patients after training |
| Habel, 2010 (34) | 30 | Social cognition | 6 | Increased activation in PFC and other regions in CT patients after training relative to CON patients |
| Bor, 2011 (62) | 32 | Executive function | 7 | Increased activation in PFC and other regions in CT patients after training relative to CON patients |
| Subramaniam, 2012 (35) | 25 | Auditory processing, visual processing, and social cognition | 16 | Increased activation in PFC in CT patients after training |
| Hooker, 2012[a] (36) | 22 | Auditory-based cognition and social cognition | 10 | Altered activation across PFC and other regions in CT patients after training relative to CON patients |
| Hooker, 2013[a] (37) | 22 | Auditory-based cognition and social cognition | 10 | Altered activation across PFC and other regions in CT patients after training relative to CON patients |
| Vianin, 2014 (63) | 16 | Executive function | 14 | Increased activation across multiple brain regions in CT patients after training |
| Subramaniam, 2014 (27) | 40 | Auditory/visual processing and social cognition | 16 | Increased activation in PFC in CT patients after training |
| Keshavan, 2017 (26) | 41 | Executive function, memory, and social cognition | >104 | Increased activation in PFC in CT patients relative to CON patients from baseline to year 2 |
| Ramsay, 2017 (38) | 26 | Executive function | 16 | Increased activation in PFC and precentral gyrus in CT patients relative to CON patients from baseline to year 2 |
| Guimond, 2018 (41) | 15 | Semantic association memory | 2 | Increased activation in PFC in CT patients after training |

CON, control program; CT, cognitive training program; PFC, prefrontal cortex.
[a]These studies used the same sample.

parietal cortex, and precuneus. Within the right parietal lobe (seven peaks), increased BOLD response was reported in the angular gyrus, inferior parietal cortex, postcentral gyrus, superior parietal cortex, and supramarginal gyrus. Left occipital regions (four peaks) included the lingual gyrus, middle occipital gyrus, and superior occipital gyrus, while right occipital regions included the inferior occipital gyrus and lingual gyrus. Finally, temporal regions (three peaks) included the bilateral amygdala and superior temporal gyrus/Heschl's gyrus.

Other brain regions reporting increased BOLD response included the left cerebellum, left insula, left paracentral lobule, bilateral supplementary motor area, right globus pallidus, right nucleus basalis, right putamen, and bilateral precentral gyrus. Decreased BOLD response was reported in only a minority of studies, including left hemispheric regions such as the superior and middle temporal gyrus, superior occipital gyrus, gyrus rectus, superior frontal gyrus/anterior cingulate gyrus, middle frontal gyrus, and thalamus/pulvinar. Only one region in the right hemisphere showed decreased BOLD response: the right thalamus/pulvinar.

Importantly, measures of brain function or structure were associated with behavioral improvements or improved outcomes across 18 of the studies identified, providing further evidence that these brain regions are associated with cognitive remediation (10,25–28,30–42).

## ALE Meta-analysis

ALE meta-analysis of the 14 studies examining changes in task-evoked BOLD response revealed no clusters showing significant overlap between two or more studies, indicating that CT had broad rather than specific effects on task-evoked BOLD response across the brain based on current research. Figure 2 shows coordinates of maxima from clusters showing effects of CT from each of these studies overlaid onto a standard brain template, indicating the wide breadth of brain regions affected by CT across these 14 studies.

Studies by Rowland *et al.* (43) and Edwards *et al.* (33) consisted of strategy training on the same task that participants were tested on. Thus, these studies were not examining generalization of training to untrained tasks but rather were examining whether strategy training could improve task performance in a short period of time. As such, these studies were possibly examining different neurophysiological processes than the other 12 studies included in the ALE analysis. As a result, the ALE analysis was

**Table 2. Structural and Functional Neuroimaging Studies of Cognitive Training in Schizophrenia Included in Systematic Review But Excluded From Activation Likelihood Estimation Meta-analysis**

| First Author and Year (Reference) | *N* | Cognitive Process(es) Targeted | Weeks | Main Outcome(s) |
|---|---|---|---|---|
| Wykes, 1998 (64) | 2 | Executive function | 12 | Altered activation across multiple regions in CT patients after training |
| Penadés, 2000 (65) | 2 | Executive function, memory, and social cognition | 12 | Increased frontal activation in one CT patient after training |
| Wexler, 2000 (31) | 8 | Auditory verbal memory | 10 | Increased activation in PFC in CT patients who showed performance gains after training |
| Penadés, 2002 (66) | 8 | Executive function, memory, and social cognition | 12 | Increased activation in PFC in CT patients after training |
| Eack, 2010[a] (23) | 53 | Executive function, memory, and social cognition | ~104 | Increased preservation of gray matter volume in multiple regions in CT patients after training |
| Keshavan, 2011[a] (24) | 50 | Executive function, memory, and social cognition | ~104 | Increased baseline cortical surface area predictive of improved cognition in CT patients after training |
| Penadés, 2013[b] (10) | 45 | Executive function | 16 | Altered functional and structural connectivity in CT patients after training |
| Penadés, 2016[b] (28) | 45 | Executive function | ~16 | Increased baseline cortical thickness across multiple regions associated with responsiveness to training in CT patients after training |
| Sestini, 2016 (67) | 17 | Social skills training | ~52 | Increased resting cerebral blood flow across multiple regions in CT patients after training |
| Eack, 2016[a] (25) | 41 | Executive function, memory, and social cognition | >104 | Altered functional connectivity in CT patients relative to CON patients from baseline to year 2 |
| Gabbatore, 2017 (68) | 1 | Executive function, language, and social cognition | 10 | Stronger amplitude of low-frequency fluctuation signal in CT patient after training |
| Ramsay, 2017 (39) | 26 | Executive function and memory | 16 | Increased thalamus connectivity in CT patients relative to CON patients from baseline to posttraining |
| Papiol, 2017 (29) | 64 | Executive function and memory | 6 | Altered hippocampal volume in CT plus aerobic exercise patients with larger schizophrenia genetic risk burden |
| Subramaniam, 2018 (40) | 30 | Executive, visual/auditory processing, and social cognition | ~16 | Increased white matter integrity in CT patients showing improved cognition after training |
| Ramsay, 2018 (30) | 44 | Executive function and auditory processing | 8 | Increased thalamus volume correlated with change in cognition from baseline to posttraining in CT but not CON patients |
| Donohoe, 2017 (69) | 27 | Executive function | 8 | Group (CT or CON) × time (pre- or posttraining) interaction effects on functional connectivity |
| Morimoto, 2018 (42) | 31 | Executive function and memory | 12 | Increased hippocampal volume in CT patients relative to CON patients after training |

CON, control program; CT, cognitive training program; PFC, prefrontal cortex.
[a]These studies used the same sample.
[b]These studies used the same sample.

performed again omitting these two studies. However, results were unchanged.

## DISCUSSION

This systematic review and meta-analysis examined effects of CT on brain structure and function in schizophrenia. The most commonly reported finding was increased activation of the PFC after training. However, ALE meta-analysis of a subset of fMRI studies revealed no areas showing significant overlap across studies, suggesting that current reported effects of CT are widely distributed across the brain, possibly reflecting the variety of therapy programs employed.

Reduced activation of the PFC during executive tasks is a consistent finding in schizophrenia, according to ALE meta-analyses of fMRI studies (44,45). As such, the most common finding in this review of increased prefrontal activation may represent a normalization of activation of this region in schizophrenia such that patient cortical activation approximates that observed in healthy control subjects posttreatment [based on studies that included healthy participants (32,34)].

Although increased prefrontal activation was the most common finding, ALE meta-analysis revealed no statistically significant overlap between specific brain regions responding to CT, whether in the PFC or beyond it. Indeed, effects of CT were reported across several brain regions, including parietal, occipital, temporal, and limbic regions, suggesting that many brain regions important for cognition and emotion may be sensitive to effects of CT. In some cases, the effect of CT on these regions likely reflects the type of training employed. For example, Hooker *et al.*'s (37) finding of increased amygdala activation after training likely reflects the use of a training

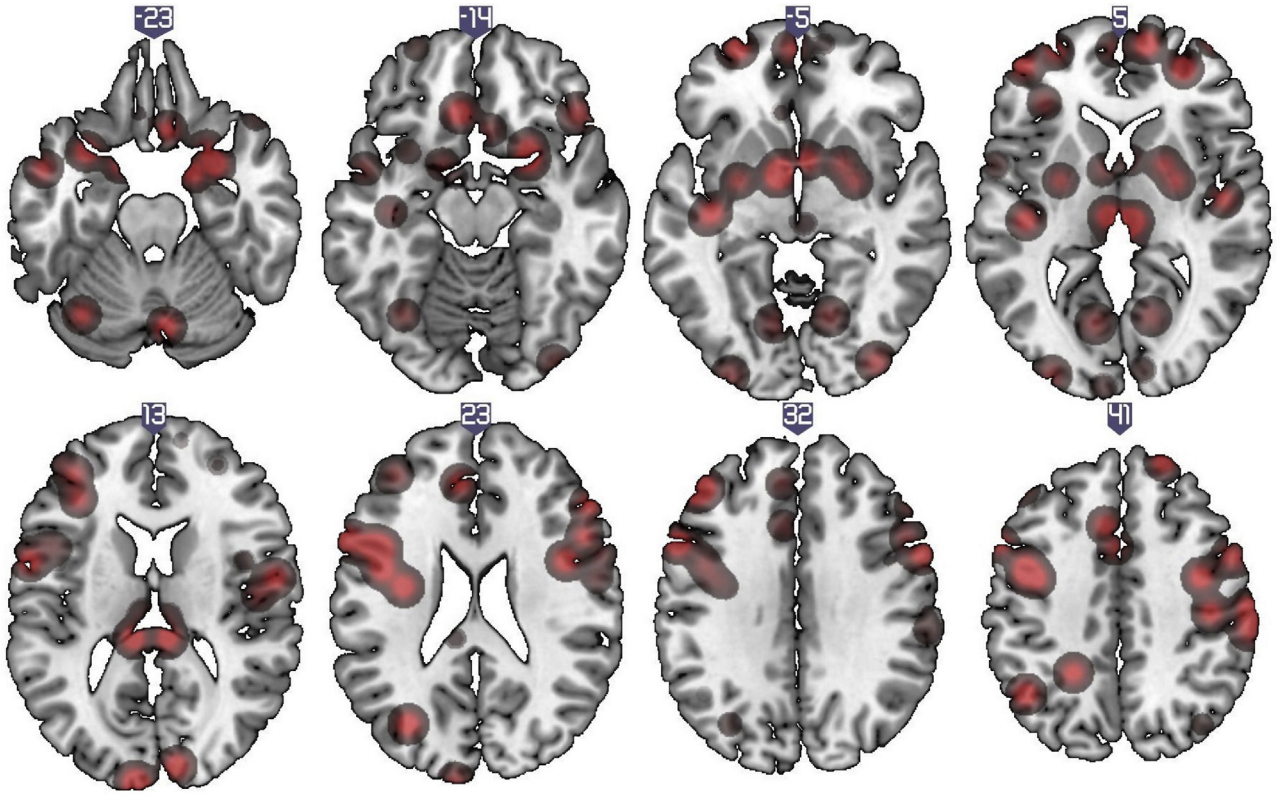


**Figure 2.** Coordinates of maxima from clusters showing effects of cognitive training across 14 functional magnetic resonance imaging studies overlaid onto a standard brain template. Each two-dimensional axial slice is labeled with a Montreal Neurological Institute coordinate. Clusters are rendered on the ch256 brain template using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). Additional editing of the figure (e.g., changing the size or resolution) was performed using MS Paint (https://support.microsoft.com/en-ie/help/4027344/windows-10-get-microsoft-paint) and Paint.NET version 3.5.10 (https://www.getpaint.net/).

program involving viewing facial displays of emotion. Thus, different types of CT may be effective for treating different types of cognitive deficit. The broad variety of training interventions used across the studies included in our meta-analysis, including differences in duration as well as content, is an important limitation and will need to be addressed by future meta-analyses. As more research is undertaken on the neural effects of CT in schizophrenia, future meta-analyses should examine effects of specific training programs on neural response to see whether specific programs are more consistent at targeting specific brain regions.

The lack of significant overlap among different studies reported by our ALE analysis contrasts with two previous ALE meta-analyses of CT in schizophrenia, both of which reported significant overlap among several studies on clusters located in several brain regions, including the PFC (13,14). However, these differences may be accounted for by the larger number of studies used in our meta-analysis (14 compared with nine) and the use of a later version of GingerALE software (2.3.6) that fixes an error that may have led to an inflated level of false positive findings in previous software versions (15). Eickhoff *et al.* (46) recommended 20 or more experiments to be included in an ALE analysis in order to have statistical power to detect moderate effects, suggesting that even our larger sample of 14 may be powered to detect only larger effects and that future ALE analyses with more studies will be required to detect smaller effects.

Although ALE has been successfully demonstrated across a large number of neuroimaging studies, it is nevertheless important to interpret results of our analysis with caution considering the differences in neuroimaging methods used across the studies we included. For example, different studies used slightly different spatial preprocessing pipelines and differed in terms of cognitive tasks, including tasks targeting working memory [e.g., (22,27,32,38)], emotion recognition (36,37), reality monitoring (35), and semantic encoding (41). Finally, studies differed in terms of activation thresholds, with some studies presenting data at more conservative thresholds [e.g., corrected for multiple comparisons using familywise error (35–37) or Monte Carlo simulations (26,41)] and other studies presenting uncorrected findings only [e.g., (34)]. Owing to the small number of CT fMRI studies currently available, we chose to include all available studies in the current ALE analysis. However, as a result of differences between studies, ALE results should be considered preliminary until more CT studies using similar neuroimaging methods are published and can be included.

It may be speculated that more overlap might have been observed between studies if more results at less conservative thresholds (e.g., $p < .001$, uncorrected) were included [e.g., similar to the approach taken in (36,37)] given that it is likely

that many more clusters showing effects of CT on brain activation would likely be observed at these thresholds. Thus, more CT studies reporting uncorrected findings in addition to corrected findings might be informative for future ALE meta-analyses.

The lack of any one specific brain region showing consistent effects across a large number of the studies also prevented us from carrying out meta-analytic connectivity modeling, a meta-analytic method that examines coactivation of brain areas with a target region of interest that shows consistent activation across studies, providing a meta-analytic measure of functional connectivity (47). Future meta-analyses using meta-analytic connectivity modeling, and future meta-analyses including functional connectivity CT studies (10), could examine consistent CT effects on functional connectivity between brain regions, which is likely to be more informative considering the role of distributed neural systems involving multiple brain regions in the types of cognitive operations targeted by CT.

All studies reported in our systematic review and meta-analysis reported positive neural effects of CT in individuals with schizophrenia. However, it should be expected that at least some studies would have null findings by chance alone. The lack of null findings suggests potential publication bias in the fMRI CT schizophrenia literature, which is typically assessed by examining effect sizes and sample sizes. For example, publication bias would be suggested if certain effects were largely driven by smaller studies. ALE meta-analysis examines spatial convergence between fMRI findings rather than effect sizes, and as such an important limitation of this method is that it cannot test for publication bias (48).

Another potential limitation with the current ALE analysis is the inclusion of both within-participant effects of CT and effects of CT in patients relative to one or more control groups. The latter effects may require more statistical power, which may result in less statistically significant findings being reported for these studies relative to the studies examining within-participant effects. This could potentially introduce a small bias in the ALE findings in favor of within-participant effects. Given the small number of studies in each category ($n$ = 7), we decided to include both effects in our overall ALE analysis. Similarly, we included effects observed at a whole-brain level ($n$ = 6), as well as effects observed within a priori defined regions of interest ($n$ = 8) owing to the small number of studies reporting findings at each of these levels. Nevertheless, as more CT imaging studies are published, future meta-analyses should examine these types of findings separately to ensure that more similar methods are being compared.

The neurophysiological mechanisms underlying CT-related effects reported across these studies are currently unknown. Likely candidates that mediate the effects of these changes include the dopamine system, given its relevance to working memory performance and neuronal plasticity (49,50), and the *N*-methyl-D-aspartate system (51). For dopamine, one hypothesis is that the prefrontal changes observed reflect changes in $D_1$ and $D_2$ receptor binding potential. McNab *et al.* (52) reported that following 14 hours of working memory training in healthy young adult men, a correlation was observed between increased working memory performance and reduced ventrolateral and dorsolateral PFC $D_1$ receptor binding but not $D_2$ receptor binding. In a later study by Backman *et al.* (49), however, reduced $D_2$ binding was also observed; this study differed from McNab *et al.* (52) in that positron emission tomography scanning was conducted during working memory performance rather than during rest. In the context of schizophrenia, these correlations with dopamine receptor binding are salient given the observed correlation between reduced working memory performance and increased $D_1$ density (53). The underlying mechanisms responsible for these training-related changes in receptor densities are not known. Whether these dopamine changes are causally related to improvements in cognitive function (e.g., via a long-term adjustment in dopamine receptor availability due to prolonged increase of endogenous dopamine during training) or instead represent the tuning effects of other transmitters [e.g., *N*-methyl-D-aspartate receptor–mediated regulation of $D_1$ receptors (54)] remains unclear. Similarly, it is likely that other neurotransmitters play a role in the neural mechanisms underlying CT effects, including gamma-aminobutyric acid and acetylcholine, which play an important role in synaptic plasticity (55,56), and it is likely that dopamine findings are a result of more studies examining this particular neurotransmitter.

Studies examining pharmacological augmented cognitive training might also be useful at identifying important mechanisms underlying responses to cognitive therapy in schizophrenia (57). For example, pharmacological augmented cognitive training might increase activation in a more select set of brain regions compared with CT on its own. A number of pharmacological agents have been tested in studies examining cognitive therapy or CT in schizophrenia, including the *N*-methyl-D-aspartate agonist D-cycloserine (58) and the wakefulness-promoting drug modafinil (59), both of which are reported to enhance learning and cognition in nonhuman animal models, although results in schizophrenia currently are largely inconclusive.

Another important question is whether changes reported across these studies reflect restorative effects or compensatory effects. For example, Bon and Franck (60) recently compared effects of different CT approaches on neural activity in schizophrenia in a review of the MRI literature. Specifically, they compared CT approaches focused on improving specific functions and CT approaches focused on learning methods to compensate for cognitive deficits. Overall, strategy approaches were associated with effects on a broader range of brain areas, possibly owing to more brain areas being recruited to carry out compensatory strategies. As more CT imaging studies are published, future studies will be able to compare effects of these different approaches using quantitative methods such as ALE as well as comparing different CT approaches based on specific cognitive functions targeted (e.g., executive function compared with social cognition).

A majority of studies included in the current review and meta-analysis were not sufficiently powered to detect small to moderate effects of CT on brain structure or function, effects similar in magnitude to many of those reported in the neuropsychological CT literature (11). As such, additional effects of CT on brain structure and function are likely to have been overlooked. This literature could be extended by larger CT imaging studies as well as meta-analyses of CT imaging

studies that include data acquired and processed using similar methods (61).

In conclusion, our systematic review and meta-analysis examined effects of various CT programs for schizophrenia on brain structure and function, with increased activation of the left PFC after training being the most frequently observed finding. However, CT effects were also widely distributed across both cortical and subcortical regions, and ALE meta-analysis on a subset of 14 fMRI studies revealed no brain regions showing statistically significant overlap across different studies. Future meta-analyses should examine common effects of studies using the same or more similar CT programs, as well as directly comparing effects between different types of CT programs, as more studies are published.

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## REFERENCES

1. Green MF (2016): Impact of cognitive and social cognitive impairment on functional outcomes in patients with schizophrenia. J Clin Psychiatry 77:8–11.
2. Schaefer J, Giangrande E, Weinberger DR, Dickinson D (2013): The global cognitive impairment in schizophrenia: Consistent over decades and around the world. Schizophr Res 150:42–50.
3. Li H, Chan RCK, McAlonan GM, Gong Q (2010): Facial emotion processing in schizophrenia: A meta-analysis of functional neuroimaging data. Schizophr Bull 36:1029–1039.
4. Kucharska-Pietura K, Mortimer A (2013): Can antipsychotics improve social cognition in patients with schizophrenia? CNS Drugs 27:335–343.
5. Hill SK, Bishop JR, Palumbo D, Sweeney JA (2010): Effect of second-generation antipsychotics on cognition: Current issues and future challenges. Expert Rev Neurother 10:43–57.
6. Choi K-H, Kwon J-H (2006): Social cognition enhancement training for schizophrenia: A preliminary randomized controlled trial. Community Ment Health J 42:177–187.
7. Minzenberg MJ, Carter CS (2012): Developing treatments for impaired cognition in schizophrenia. Trends Cogn Sci 16:35–42.
8. Insel TR, Gogtay N (2014): National Institute of Mental Health clinical trials: New opportunities, new expectations. JAMA Psychiatry 71:745–746.
9. Katsnelson A (2014): The modelling challenge. Nature 508:S8–S9.
10. Penadés R, Pujol N, Catalán R, Massana G, Rametti G, García-Rizo C, *et al.* (2013): Brain effects of cognitive remediation therapy in schizophrenia: A structural and functional neuroimaging study. Biol Psychiatry 73:1015–1023.
11. Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P (2011): A meta-analysis of cognitive remediation for schizophrenia: Methodology and effect sizes. Am J Psychiatry 168:472–485.
12. Lage C, Wiles K, Shergill SS, Tracy DK (2016): A systematic review of the effects of low-frequency repetitive transcranial magnetic stimulation on cognition. J Neural Transm 123:1479–1490.
13. Ramsay IS, MacDonald AW III (2015): Brain correlates of cognitive remediation in schizophrenia: Activation likelihood analysis shows preliminary evidence of neural target engagement. Schizophr Bull 41:1276–1284.
14. Wei Y-Y, Wang J-J, Yan C, Li ZQ, Pan X, Cui Y, *et al.* (2016): Correlation between brain activation changes and cognitive improvement following cognitive remediation therapy in schizophrenia: An activation likelihood estimation meta-analysis. Chin Med J (Engl) 129:578–585.
15. Eickhoff SB, Laird AR, Fox PM, Lancaster JL, Fox PT (2017): Implementation errors in the GingerALE software: Description and recommendations. Hum Brain Mapp 38:7–11.
16. Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT (2009): Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: A random-effects approach based on empirical estimates of spatial uncertainty. Hum Brain Mapp 30:2907–2926.
17. Turkeltaub PE, Eickhoff SB, Laird AR, Fox M, Wiener M, Fox P (2012): Minimizing within-experiment and within-group effects in activation likelihood estimation meta-analyses. Hum Brain Mapp 33:1–13.
18. Eickhoff SB, Bzdok D, Laird AR, Kurth F, Fox PT (2012): Activation likelihood estimation meta-analysis revisited. NeuroImage 59:2349–2361.
19. Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL, *et al.* (2005): ALE meta-analysis: Controlling the false discovery rate and performing statistical contrasts. Hum Brain Mapp 25:155–164.
20. Wagner S, Sebastian A, Lieb K, Tüscher O, Tadić A (2014): A coordinate-based ALE functional MRI meta-analysis of brain activation during verbal fluency tasks in healthy control subjects. BMC Neurosci 15:19.
21. Faul F, Erdfelder E, Lang A-G, Buchner A (2007): G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 39:175–191.
22. Wykes T, Brammer M, Mellers J, Bray P, Reeder C, Williams C, Corner J (2002): Effects on the brain of a psychological treatment: Cognitive remediation therapy—Functional magnetic resonance imaging in schizophrenia. Br J Psychiatry 181:144–152.
23. Eack SM, Hogarty GE, Cho RY, Prasad KM, Greenwald DP, Hogarty SS, *et al.* (2010): Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: Results from a 2-year randomized controlled trial. Arch Gen Psychiatry 67:674–682.
24. Keshavan MS, Eack SM, Wojtalik JA, Prasad KM, Francis AN, Bhojraj TS, *et al.* (2011): A broad cortical reserve accelerates response to cognitive enhancement therapy in early course schizophrenia. Schizophr Res 130:123–129.
25. Eack SM, Newhill CE, Keshavan MS (2016): Cognitive enhancement therapy improves resting-state functional connectivity in early course schizophrenia. J Soc Social Work Res 7:211–230.
26. Keshavan MS, Eack SM, Prasad KM, Haller CS, Cho RY (2017): Longitudinal functional brain imaging study in early course schizophrenia before and after cognitive enhancement therapy. NeuroImage 151:55–64.
27. Subramaniam K, Luks TL, Garrett C, Chung C, Fisher M, Nagarajan S, *et al.* (2014): Intensive cognitive training in schizophrenia enhances working memory and associated prefrontal cortical efficiency in a manner that drives long-term functional gains. NeuroImage 99:281–292.
28. Penadés R, Pujol N, Catalán R, Masana G, García-Rizo C, Bargalló N, *et al.* (2016): Cortical thickness in regions of frontal and temporal lobes is associated with responsiveness to cognitive remediation therapy in schizophrenia. Schizophr Res 171:110–116.
29. Papiol S, Popovic D, Keeser D, Hasan A, Schneider-Axmann T, Degenhardt F, *et al.* (2017): Polygenic risk has an impact on the structural plasticity of hippocampal subfields during aerobic exercise combined with cognitive remediation in multi-episode schizophrenia. Transl Psychiatry 7:e1159.
30. Ramsay IS, Fryer S, Boos A, Roach BJ, Fisher M, Loewy R, *et al.* (2018): Response to targeted cognitive training correlates with change in thalamic volume in a randomized trial for early schizophrenia. Neuropsychopharmacology 43:590–597.

31. Wexler BE, Anderson M, Fulbright RK, Gore JC (2000): Preliminary evidence of improved verbal working memory performance and normalization of task-related frontal lobe activation in schizophrenia following cognitive exercises. Am J Psychiatry 157:1694–1697.
32. Haut KM, Lim KO, MacDonald A III (2010): Prefrontal cortical changes following cognitive training in patients with chronic schizophrenia: Effects of practice, generalization, and specificity. Neuropsychopharmacology 35:1850–1859.
33. Edwards BG, Barch DM, Braver TS (2010): Improving prefrontal cortex function in schizophrenia through focused training of cognitive control. Front Hum Neurosci 4:32.
34. Habel U, Koch K, Kellermann T, Reske M, Frommann N, Wölwer W, *et al.* (2010): Training of affect recognition in schizophrenia: Neurobiological correlates. Soc Neurosci 5:92–104.
35. Subramaniam K, Luks TL, Fisher M, Simpson GV, Nagarajan S, Vinogradov S (2012): Computerized cognitive training restores neural activity within the reality monitoring network in schizophrenia. Neuron 73:842–853.
36. Hooker CI, Bruce L, Fisher M, Verosky SC, Miyakawa A, Vinogradov S (2012): Neural activity during emotion recognition after combined cognitive plus social cognitive training in schizophrenia. Schizophr Res 139:53–59.
37. Hooker CI, Bruce L, Fisher M, Verosky SC, Miyakawa A, D'Esposito M, *et al.* (2013): The influence of combined cognitive plus social-cognitive training on amygdala response during face emotion recognition in schizophrenia. Psychiatry Res 213:99–107.
38. Ramsay IS, Nienow TM, Marggraf MP, MacDonald AW (2017): Neuroplastic changes in patients with schizophrenia undergoing cognitive remediation: Triple-blind trial. Br J Psychiatry 210:216–222.
39. Ramsay IS, Nienow TM, MacDonald AW III (2017): Increases in intrinsic thalamocortical connectivity and overall cognition following cognitive remediation in chronic schizophrenia. Biol Psychiatry Cogn Neurosci Neuroimaging 2:355–362.
40. Subramaniam K, Gill J, Fisher M, Mukherjee P, Nagarajan S, Vinogradov S (2018): White matter microstructure predicts cognitive training-induced improvements in attention and executive functioning in schizophrenia. Schizophr Res 193:276–283.
41. Guimond S, Béland S, Lepage M (2018): Strategy for semantic association memory (SESAME) training: Effects on brain functioning in schizophrenia. Psychiatry Res 271:50–58.
42. Morimoto T, Matsuda Y, Matsuoka K, Yasuno F, Ikebuchi E, Kameda H, *et al.* (2018): Computer-assisted cognitive remediation therapy increases hippocampal volume in patients with schizophrenia: A randomized controlled trial. BMC Psychiatry 18:83.
43. Rowland LM, Griego JA, Spieker EA, Cortes CR, Holcomb HH (2010): Neural changes associated with relational learning in schizophrenia. Schizophr Bull 36:496–503.
44. Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, *et al.* (2005): Beyond hypofrontality: A quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. Hum Brain Mapp 25:60–69.
45. Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC (2009): Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry 66:811–822.
46. Eickhoff SB, Nichols TE, Laird AR, Hoffstaedter F, Amunts K, Fox PT, *et al.* (2016): Behavior, sensitivity, and power of activation likelihood estimation characterized by massive empirical simulation. NeuroImage 137:70–85.
47. Robinson JL, Laird AR, Glahn DC, Lovallo WR, Fox PT (2010): Meta-analytic connectivity modeling: Delineating the functional connectivity of the human amygdala. Hum Brain Mapp 31:173–184.
48. Müller VI, Cieslik EC, Laird AR, Fox PT, Radua J, Mataix-Cols D, *et al.* (2018): Ten simple rules for neuroimaging meta-analysis. Neurosci Biobehav Rev 84:151–161.
49. Bäckman L, Nyberg L, Soveri A, Johansson J, Andersson M, Dahlin E, *et al.* (2011): Effects of working-memory training on striatal dopamine release. Science 333:718.
50. Bäckman L, Nyberg L (2013): Dopamine and training-related working-memory improvement. Neurosci Biobehav Rev 37:2209–2219.
51. Guo N, Hwang D-R, Lo E-S, Huang Y-Y, Laruelle M, Abi-Dargham A (2003): Dopamine depletion and in vivo binding of PET D1 receptor radioligands: Implications for imaging studies in schizophrenia. Neuropsychopharmacology 28:1703–1711.
52. McNab F, Varrone A, Farde L, Jucaite A, Bystritsky P, Forssberg H (2009): Changes in cortical dopamine D1 receptor binding associated with cognitive training. Science 323:800–802.
53. Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, *et al.* (2002): Prefrontal dopamine D1 receptors and working memory in schizophrenia. J Neurosci 22:3708–3719.
54. Scott L, Kruse MS, Forssberg H, Brismar H, Greengard P, Aperia A (2002): Selective up-regulation of dopamine D1 receptors in dendritic spines by NMDA receptor activation. Proc Natl Acad Sci U S A 99:1661–1664.
55. Barberis A, Bacci A (2015): Plasticity of GABAergic synapses. Front Cell Neurosci 9:262.
56. Rasmusson DD (2000): The role of acetylcholine in cortical synaptic plasticity. Behav Brain Res 115:205–218.
57. Swerdlow NR (2012): Beyond antipsychotics: Pharmacologically-augmented cognitive therapies (PACTs) for schizophrenia. Neuropsychopharmacology 37:310–311.
58. Gorrlieb JD, Cather C, Shanahan M, Creedon T, Macklin EA, Goff DC (2011): D-cycloserine facilitation of cognitive behavioral therapy for delusions in schizophrenia. Schizophr Res 131:69–74.
59. Michalopoulou PG, Lewis SW, Drake RJ, Reichenberg A, Emsley R, Kalpakidou AK, *et al.* (2015): Modafinil combined with cognitive training: Pharmacological augmentation of cognitive training in schizophrenia. Eur Neuropsychopharmacol 25:1178–1189.
60. Bon L, Franck N (2018): The impact of cognitive remediation on cerebral activity in schizophrenia: Systematic review of the literature. Brain Behav 8:e908.
61. Thompson PM, Stein JL, Medland SE, Hibar DP, Vasquez AA, Renteria ME, *et al.* (2014): The ENIGMA Consortium: Large-scale collaborative analyses of neuroimaging and genetic data. Brain Imaging Behav 8:153–182.
62. Bor J, Brunelin J, d'Amato T, Costes N, Suaud-Chagny M-F, Saoud M, *et al.* (2011): How can cognitive remediation therapy modulate brain activations in schizophrenia? An fMRI study. Psychiatry Res 192:160–166.
63. Vianin P, Urben S, Magistretti P, Marquet P, Fornari E, Jaugey L (2014): Increased activation in Broca's area after cognitive remediation in schizophrenia. Psychiatry Res 221:204–209.
64. Wykes T (1998): What are we changing with neurocognitive rehabilitation? Illustrations from two single cases of changes in neuropsychological performance and brain systems as measured by SPECT. Schizophr Res 34:77–86.
65. Penadés R, Boget T, Lomeña F, Bernardo M, Mateos JJ, Laterza C, *et al.* (2000): Brain perfusion and neuropsychological changes in schizophrenic patients after cognitive rehabilitation. Psychiatry Res 98:127–132.
66. Penadés R, Boget T, Lomena F, Mateos J, Catalan R, Gasto C, *et al.* (2002): Could the hypofrontality pattern in schizophrenia be modified through neuropsychological rehabilitation? Acta Psychiatr Scand 105:202–208.
67. Sestini S, Perone R, Domenichetti S, Mazzeo C, Massai V, Rispoli A (2016): Brain network underlying the improvement of social functioning in schizophrenic patients after one-year treatment with social skills training. Curr Radiopharm 9:150–159.
68. Gabbatore I, Bosco FM, Geda E, Gastaldo L, Duca S, Costa T, *et al.* (2017): Cognitive pragmatic rehabilitation program in schizophrenia: A single case fMRI study. Neural Plast 2017:1612078.
69. Donohoe G, Dillon R, Hargreaves A, Mothersill O, Castorina M, Furey E, *et al.* (2017): Effectiveness of a low support, remotely accessible, cognitive remediation training programme for chronic psychosis: Cognitive, functional and cortical outcomes from a single blind randomised controlled trial. Psychol Med 48:751–764.