**Title page**

**Manuscript title:** 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 behaviourally based cognitive training programmes, 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 which a majority (16) were functional neuroimaging studies. 15 of these studies reported increased neural activation following cognitive training, with increased left prefrontal activation 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 programmes used.

**Introduction**

Cognitive dysfunction is a core feature of schizophrenia and a strong predictor of employment, relationships, and independent living (1). Cognitive deficits include problems with short-term memory, attention and reasoning, as well as social cognitive abilities such as recognising facial displays of emotion (2-3). To date, efforts to target these deficits pharmacologically have, however, 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, behaviourally based cognitive training (CT) approaches have become a substantial research focus. CT (or cognitive remediation therapy, CRT) 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 programmes may be administered via pen and paper or through specialised computer software, on a regular basis and over a period of weeks. In schizophrenia, meta-analysis in over 2,000 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 programmes are effective, by showing that they have an impact that can be observed at the level of brain as well as behaviour. Better understanding of the neural mechanisms underlying CT may also help inform future studies which seek to combine CT with other brain-based interventions, e.g. pharmacological interventions, or repetitive transcranial magnetic stimulation (rTMS), 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 & McDonald (13) reported what they described as ‘preliminary’ evidence of increased activation in the lateral and medial prefrontal cortex (PFC), parietal cortex, insula, and the caudate and thalamus following CT programs that were based on a variety of approaches. Since then, many new CT studies that have included neuroimaging have been reported. In addition, the meta-analytic approach taken in the Ramsay & McDonald study, and 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 MRI studies of CT in schizophrenia now reported, and the limitations of previous meta-analytic strategies, the purpose of the present study was to undertake a systematic review and meta-analysis of all CT studies in schizophrenia that have included neuroimaging so far so as 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 cognitive training programme in patients with schizophrenia. This search, which included all papers 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)”. 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 papers 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, and the reasons for inclusion or 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.

>>Figure 1<<

Next, we used the activation likelihood estimation (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 (SPECT) studies (N = 4), studies including volumetric measures (N = 5), measures of cortical surface area (N = 1), diffusion tensor imaging (DTI) (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. Schizophrenia patients showed altered task-evoked BOLD response after a training period relative to before (N = 7), or

2. Schizophrenia patients 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** summarises the main outcomes from the studies included in both our systematic review and ALE meta-analysis (N = 14). **Table 2** summarises the main outcomes from the studies included in our systematic review only (N = 17). **Supplementary table 1** summarises the main outcomes in more detail for all 31 studies included in our systematic review, including those also included in our ALE meta-analysis.

>>Table 1<<

>>Table 2<<

Maps of altered task-evoked BOLD response were created for each study by modelling individual coordinates as Gaussian functions. The width of each of these functions is calculated by GingerALE software based on each study's sample size, i.e. 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 < 0.001, uncorrected (cluster-forming threshold), and then cluster-thresholded using 1000 threshold permutations and a cluster-level threshold of p < 0.05, 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, e.g. meta-analysis of CRT 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 = 0.05. 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≤6 receiving the intervention) and only one of these (22) included a control group.

In terms of the CRT approaches studied, 9 studies specified their focus as being on executive function, with targeted training of executive sub-processes that included attention, working memory, planning, problem solving, logical thinking and cognitive shift. 3 additional studies examined effects of programmes that focused on memory, including auditory verbal memory, relational memory, and semantic association memory, 2 studies examined only social cognition or social skills training, and 17 studies examined effects of programmes 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 programmes employed were reported to have been administered by a variety of means, including pen and paper, specialised computer software, and/or interactions with other individuals (e.g. in group sessions).

The mean sample size was 28.32 (standard deviation = 15.66) across the 31 studies. 9 studies reported sample sizes greater than 41, the sample size identified in our power analysis as the minimum required to identified effects similar to those reported in the neuropsychological literature (10, 23-24, 26-31).

Regarding the 14 studies included in the ALE meta-analysis only, 5 studies specified their focus as being on executive function, 2 studies focussed on memory (including relational memory and semantic memory), 1 study focussed on social cognition, and 6 studies examined effects of programmes 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 (standard deviation = 8.45) across the 14 studies. Only 2 studies included in the ALE meta-analysis reported sample sizes greater than 41.

**Neuroimaging findings:** The most common finding across studies was increased prefrontal activation, indexed as either increased cerebral blood flow (CBF) or increased BOLD response (16 studies - 9 studies showing increased prefrontal activation in CT patients after training, and 7 studies 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 prefrontal cortex (16 activation peaks reported in MNI or Talairach coordinates), including the cingulate, dorsal prefrontal cortex, dorsolateral prefrontal cortex, frontopolar cortex, inferior frontal gyrus, inferior frontal operculum, inferior/middle frontal gyrus, medial prefrontal cortex, and middle frontal gyrus. The second most common finding was of increased BOLD response in the right prefrontal cortex (9 peaks), including the dorsal prefrontal cortex, dorsolateral prefrontal cortex, frontopolar cortex, gyrus rectus/medial orbitofrontal cortex, inferior frontal gyrus, superior frontal gyrus, and superior frontal gyrus/media prefrontal cortex.

Within the left parietal lobe (4 peaks), increased BOLD response was reported in the left angular gyrus, left inferior parietal cortex, and precuneus, and within the right parietal lobe (7 peaks), increased BOLD response was reported in the angular gyrus, inferior parietal cortex, postcentral gyrus, superior parietal cortex and supramarginal gyrus. Left occipital regions (4 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 (3 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 nucleaus basalis, right putamen, and bilateral precentral gyrus. Decreased BOLD response was only reported in 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 behavioural improvements or improved outcomes across 18 of the studies identified, providing further evidence that these brain regions are associated with cognitive remediation (10, 26-29, 31-43). Specific findings from each study, including MNI coordinates, are presented in **Supplementary table 1**.

**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 breath of brain regions affected by CT across these 14 studies.

>>Figure 2<<

Rowland et al. (55), and Edwards et al. (34) consisted of strategy training on the same task that participants were tested on. Thus, these studies were not examining generalisation of training to untrained tasks but rather whether strategy training could improve task performance in a short space of time. As such, these studies are possibly examining different neurophysiological processes to the other 12 studies included in the ALE analysis. As a result, the ALE analysis was performed again omitting these two studies. However, results were unchanged.

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 each of the studies we included. For example, different studies used slightly different spatial pre-processing pipelines, even though most studies followed a broadly similar pipeline including motion correction, warping to a standard brain template, and smoothing. Studies also differed in terms of cognitive tasks, including tasks targeting working memory, relational learning, emotion recognition, reality monitoring, verbal fluency, preparing to overcome prepotency, and semantic encoding (a full list is provided in **Supplementary Table 1**). Finally, studies differed in terms of activation thresholds, with some studies presenting data corrected for multiple comparisons using family-wise error (e.g. 36-38) or Monte Carlo simulations (27, 42), and other studies presenting uncorrected findings only (e.g. 35). Due to the small number of CT fMRI studies currently available, we chose to include all available studies in the present 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, allowing us to examine more similar studies.

**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 prefrontal cortex 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 programmes employed.

Reduced activation of the prefrontal cortex during executive tasks is a consistent finding in schizophrenia, according to ALE meta-analysis of fMRI studies (44-45). As such, the most common finding in this review of increased prefrontal activation may represent a ‘normalisation’ of activation of this region in schizophrenia, such that patient cortical activation approximates that observed in healthy controls post-treatment (based on studies that included healthy participants (33,35)).

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 prefrontal cortex 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 (38) finding of increased amygdala activation after training likely reflects the use of a training programme 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 programmes on neural response to see if specific programmes are more consistent at targeting specific brain regions. This should include programmes with similar durations and content.

The lack of significant overlap between different studies reported by our ALE analysis contrasts with two previous ALE meta-analyses of CT in schizophrenia, both of which reported significant overlap between several studies on clusters located in several brain regions, including the prefrontal cortex (13-14). However, these differences may be accounted for by the larger number of studies used in our meta-analysis (14 compared to 9) 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) now recommend 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 only be powered to detect larger effects, and suggesting future ALE analyses with more studies will be required to detect smaller effects.

In many cases, conservative statistical thresholds were used to define effects of CT on brain activation in the studies included in our ALE meta-analysis, including correction for multiple comparisons using family-wise error (e.g. 36-37) or Monte Carlo simulations (e.g. 27, 42). It may be speculated that more overlap might have been observed between studies if more results at less conservative thresholds (e.g. p < 0.001, uncorrected) were included also (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 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 modelling (MACM), a meta-analytic method that examines co-activation 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 MACM, 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. As such, it should be acknowledged that results presented may be affected by publication bias in the CT neuroimaging literature, which was not specifically tested in relation to our ALE analysis.

One 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 later 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 favour 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) due 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 (48-49), and the NMDA system (50). For dopamine, one hypothesis is that the pre-frontal changes observed reflect changes in D1 and D2 receptor binding potential. McNab et al. (51) reported that, following 14 hours of working memory training in healthy young adult males, a correlation was observed between increased working memory performance and reduced ventrolateral and dorsolateral PFC D1, but not D2 receptor binding. In a later study by Backman et al. (48), however, reduced D2 binding was also observed; this study differed from McNab et al. in that PET 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 D1 density (52). 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 rather represents the tuning effects of other transmitters (e.g. NMDA receptor mediated regulation of D1 receptors (53)) remains unclear. Similarly, it is likely that other neurotransmitter play a role in the neural mechanisms underlying CT effects, including *gamma*-Aminobutyric acid (GABA) and acetylcholine, which play an important role in synaptic plasticity (54-55), and it is likely that dopamine findings are a result of more studies examining this particular neurotransmitter.

Studies examining pharmacological augmented cognitive training (PACT) might also be useful at identifying important mechanisms underlying responses to cognitive therapy in schizophrenia (56). For example, PACT might increase activation in a more select set of brain regions compared to CT on its own. A number of pharmacological agents are been tested in studies examining cognitive therapy or cognitive training in schizophrenia, including the NMDA agonist D-cycloserine (57), and the wakefulness-promoting drug modafinil (58), both of which are reported to enhance learning and cognition in non-human animal models, although results in schizophrenia are largely inconclusive at present.

Another important question is whether changes reported across these studies reflect restorative effects or compensatory effects. For example, Bon and Franck (59) recently compared effects of different CT approaches on neural activity in schizophrenia in a review of the MRI literature. Specifically, they compared CT approaches focussed on improving specific functions, and CT approaches focussed on learning methods to compensate for cognitive deficits. Overall, strategy approaches were associated with effects on a broader range of brain areas, possibly due 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 to 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, and also meta-analyses of CT imaging studies that include data acquired and processed using similar methods, similar to the approach taken by the ENIGMA consortium to increase sample sizes in neuroimaging genetic studies by combining data across multiple sites, each using the same data processing pipeline (60).

In conclusion, our systematic review and meta-analysis examined effects of various CT programmes for schizophrenia on brain structure and function, with increased activation of the left prefrontal cortex after training the most frequently observed finding. However, CT effects were also widely distributed across both cortical and sub-cortical 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 programmes, as well as directly comparing effects between different types of CT programme, as more studies are published.

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**Disclosures**

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**Table legends**

**Table 1** – Functional magnetic resonance imaging studies of cognitive training in schizophrenia included in systematic review and activation likelihood estimation meta-analysis.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **First author** | **N** | **Cognitive processes targeted** | **Week** | **Main neural activation outcomes** |
| Wykes 2002 (22) | 18 | Executive function | 12 | Increased activation in PFCb and other regions in CTc patients after training. |
| Haut 2010 (33) | 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 (61) | 34 | Relational memory | < 1 | Altered activation across parietal, temporal and occipital lobes in CT patients after training. |
| Edwards 2010 (34) | 36 | Executive function | < 1 | Altered activation in PFC and other regions in CT patients after training. |
| Habel 2010 (35) | 30 | Social cognition | 6 | Increased activation in PFC and other regions in CT patients after training relative to CONd 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 (36) | 25 | Auditory processing, visual processing and social cognition | 16 | Increased activation in PFC in CT patients after training. |
| Hooker 2012a (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. |
| Hooker 2013a (38) | 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 (28) | 40 | Auditory/visual processing and social cognition | 16 | Increased activation in PFC in CT patients after training. |
| Keshavan 2017 (27) | 41 | Executive function, memory and social cognition | > 104 | Increased activation in PFC in CT patients relative to COM patients, from baseline to year 2. |
| Ramsay 2017a (39) | 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 (42) | 15 | Semantic association memory | 2 | Increased activation in PFC in CT patients after training. |

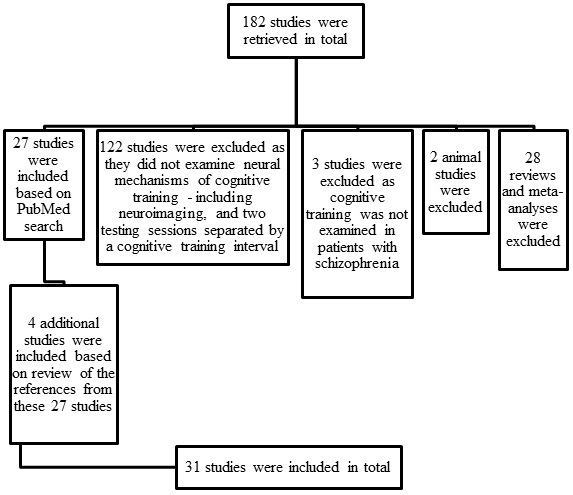
aThese studies used the same sample; bPFC = prefrontal cortex; cCT = patients who completed a cognitive training program; dCON = patients who completed a control program

**Table 2** – Structural and functional neuroimaging studies of cognitive training in schizophrenia included in systematic review but excluded from ALE meta-analysis.

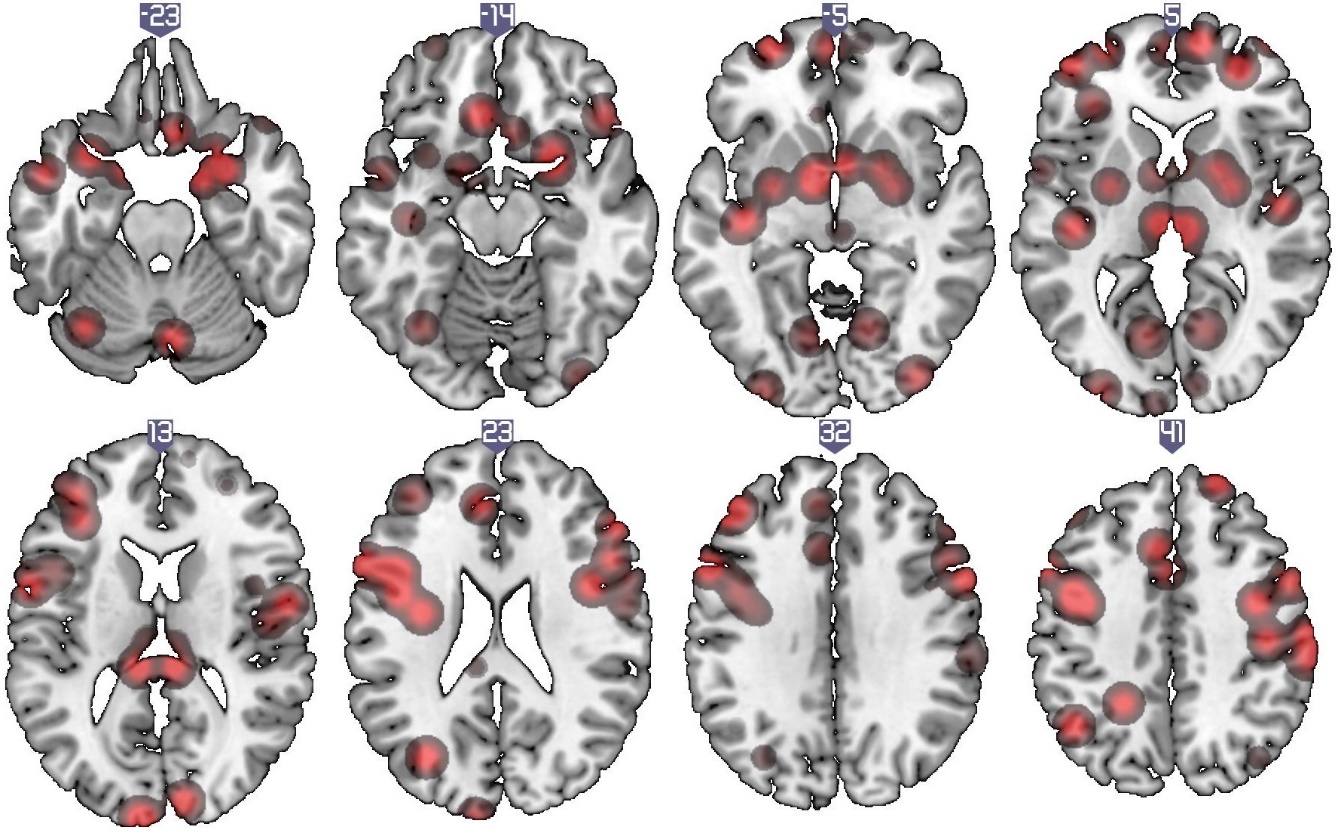
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **First author** | **N** | **Cognitive processes targeted** | **Week** | **Main outcomes** |
| Wykes 1998 (64) | 2 | Executive function | 12 | Altered activation across multiple regions in CTc patients after training. |
| Penadés 2000 (65) | 2 | Executive function, memory and social cognition | 12 | Increased frontal activation in one CT patient after training. |
| Wexler 2000 (32) | 8 | Auditory verbal memory | 10 | Increased activation in PFCd 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 2010a (23) | 53 | Executive function, memory and social cognition | ~104 | Increased preservation of grey matter volume in multiple regions in CT patients after training. |
| Keshavan 2011a (24) | 50 | Executive function, memory and social cognition | ~104 | Increased baseline cortical surface area predictive of improved cognition, CT patients. |
| Penadés 2013b (10) | 45 | Executive function | 16 | Altered functional and structural connectivity in CT patients after training. |
| Penadés 2016b (29) | 45 | Executive function | ~16 | Increased baseline cortical thickness across multiple regions associated with responsiveness to training in CT patients after training. |
| Sestini 2016 (25) | 17 | Social skills training | ~52 | Increased resting cerebral blood flow across multiple regions in CT patients after training. |
| Eack 2016a (26) | 41 | Executive function, memory and social cognition | > 104 | Altered functional connectivity in CT patients relative to CONe patients, baseline-year 2. |
| Gabbatore 2017 (67) | 1 | Executive function, language, and social cognition | 10 | Stronger amplitude of low frequency fluctuation signal in CT patient post-training. |
| Ramsay 2017b (40) | 26 | Executive function and memory | 16 | Increased thalamus connectivity in CT relative to CON patients, baseline to post-training. |
| Papiol 2017 (30) | 64 | Executive function, and memory | 6 | Altered hippocampal volume in CT plus aerobic exercise patients with larger schizophrenia genetic risk burden. |
| Subramaniam 2018 (41) | 30 | Executive, visual/ auditory processing, social cognition | ~16 | Increased white matter integrity in CT patients showing improved cognition post-training. |
| Ramsay 2018 (31) | 44 | Executive function and auditory processing | 8 | Increased thalamus volume correlated with change in cognition, baseline-post-training in CT but not CON patients |
| Donohoe 2017 (68) | 27 | Executive function | 8 | Group (CT or CON) x time (pre or post) interaction effects on functional connectivity |
| Morimoto 2018 (43) | 31 | Executive function and memory | 12 | Increased hippocampal volume in CT patients relative to CON patients after training |

aThese studies used the same sample; bThese studies used the same sample; cCT = patients who completed a cognitive training program; dPFC = prefrontal cortex; eCON = patients who completed a control program

**Figure legends:**



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

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**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 labelled 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/resolution) was performed using MS Paint and Paint.NET v3.5.10.