Neural Effects of Cognitive Remediation

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Terre brûlée au vent, des landes de pierres, autour des lacs… c’est le décor du Connemara.

Les lacs de connemara
Michel Sardou
Disclosures

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Outline

Neural effects of Cognitive remediation
1. Are structural and functional brain changes associated with CRT?
2. Ale meta-analysis: where are these changes most likely to occur?
3. Do changes in brain morphology/function mediate the effects of CRT on functional outcome?
4. Are they persistent over time?
Neuropsychological effects

Donohoe et al., (2018)
Psychological Medicine

(A) Letter Number Sequencing scaled scores

(B) Spatial working memory standard errors
Functional connectivity effects

Donohoe et al., Psychological Medicine (2018)

(a) Functional connectivity between the R precuneus (seed region in green) & the L inferior parietal lobule

(b) Functional connectivity between the L anterior cingulate cortex (seed region in green) & the R midcingulate cortex.

(a) Increased connectivity post intervention
Background: Neuroimaging studies of CRT in Psychosis

• Meta-analysis (Ramsay and MacDonald 2015, n=9): “preliminary” evidence of increased activation following CRT (various)
  • The lateral and medial prefrontal cortex (PFC), parietal cortex, insula, caudate, and thalamus.
  • Similar findings reported in Wei et al. (2016).

• Meta-analysis approach taken: activation likelihood estimation (ALE):
  • Showed evidence of inflated rate of statistically significant regional activations across studies.
  • ALE has since been updated.
• Use the updated ALE toolbox to undertake a meta-analysis of all studies now available
  → More studies.
  → More accurate software package.
  → More accurate picture of which cortical regions are most consistently implicated.

Archival Report


David Mothersill and Gary Donohoe

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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Methods: Activation Likelihood Estimation (ALE)

• Any single fMRI study can highlight the brain activity that occurs in response to a specific task, in a specific MRI scanner environment.

• But combining data from multiple, independent studies gives us a measure of the robustness of the activation patterns we observe.

• Activation Likelihood Estimation (ALE) is a meta-analytic procedure that uses coordinates of activation from multiple fMRI studies to estimate the probability of effects occurring across more than one study. I.e. Does the same blob light up in each study?

Eickhoff et al. (2017): Hum Brain Mapp 38:7–11.
Methods: Study inclusion

• Up to December 2018

• 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)
Results: Systematic review

- Based on 31 studies published to date.
- Average time training ~47.4 hours
- Average sample size ~28.3
- Studies carried out prior to 2005: based on very small samples (n < 6 receiving intervention).

Multiple brain regions implicated

(Included in systematic review but not Meta-analysis)
Results: ALE meta-analysis

• Of N=31 studies, 16 were fMRI studies, of which 14 were included in ALE meta-analysis.

• 15/16 reported increased neural activation following training.

• Increased neural activation was generally associated with improved cognitive function.

<table>
<thead>
<tr>
<th>First Author and Year (Reference)</th>
<th>N</th>
<th>Cognitive Process(es) Targeted</th>
<th>Weeks</th>
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<tbody>
<tr>
<td>Wykes, 2002 (22)</td>
<td>18</td>
<td>Executive function</td>
<td>12</td>
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<td>Haert, 2010 (33)</td>
<td>27</td>
<td>Executive function and memory</td>
<td>4-6</td>
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<td>Rowland, 2010 (43)</td>
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<td>Edwards, 2010 (33)</td>
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<td>Habel, 2010 (34)</td>
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<td>Social cognition</td>
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<td>Bor, 2011 (62)</td>
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<td>Executive function</td>
<td>7</td>
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<td>Subramaniam, 2012 (35)</td>
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<td>Auditory processing, visual processing, and social cognition</td>
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<td>Hooker, 2012 (36)</td>
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<td>Subramaniam, 2014 (27)</td>
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<td>Auditory/visual processing and social cognition</td>
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<td>Keshavan, 2017 (26)</td>
<td>41</td>
<td>Executive function, memory, and social cognition</td>
<td>&gt;104</td>
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<td>Ramsay, 2017 (38)</td>
<td>26</td>
<td>Executive function</td>
<td>16</td>
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<tr>
<td>Guimond, 2018 (41)</td>
<td>15</td>
<td>Semantic association memory</td>
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</table>

Average sample size ~27.4
Average time training ~43.7 hours/15.7 weeks
Results: Most common findings

- Increased **LEFT** prefrontal activation was the most frequently observed finding (16 activation peaks).

- Increased **RIGHT** prefrontal activation was the 2\textsuperscript{nd} most frequently observed finding (9 activation peaks).

- Activation peaks varied by study, including:
  - Left hemisphere: cingulate, inferior frontal operculum, middle frontal gyrus.
  - Both Hemispheres: dorsal PFC, DLPFC, frontopolar cortex, inferior frontal gyrus, medial PFC.

- Increase **LEFT** parietal 3\textsuperscript{rd} most frequently observed (4 peaks).

*Activation peak = Brain region where brain activation is maximal.*
Results: ALE Meta-analysis

- No specific brain regions showing consistent effects.
  → no clusters showed overlap between two or more studies.

- This pattern of results suggested a broader, more distributed pattern of effects.

Coordinates of maxima from clusters showing effects of cognitive training across 14 fMRI studies overlaid onto a standard brain template.
Studies published since our Meta-analysis

Functional MRI:

- Penades (2020) [n=26] Both CRT group and a combined CRT/SST group showed altered (reduced) connectivity between sensorimotor network and lingual gyrus and occipital fusiform gyrus.


Longitudinal effects of CRT on brain structure


- Eack 2010 (n=23 v 19): At 2 yr follow-up, CT associated with preserved GM volume of the left hippocampus, parahippocampal gyrus, and fusiform gyrus, and increased GM in amygdala. These effects mediated beneficial effects of CT.

- Eack et al 2016, Keshevan et al 2020 (n=25v16): At 2yr follow up, CT associated with increased BOLD activity in the right dorsolateral prefrontal cortex (DLPFC) and anterior cingulate, and reduced connectivity between these regions. This was in turn associated with improved cognition.
CAN MRI predict response?

Structural MRI:

• Takahashi et al (2020): [N=21 SZ + 23 controls]
  • Lower baseline cortical thickness of the right lateral prefrontal cortex at baseline associated with
greater improvement in social function at 12 weeks. No change in cortical thickness following
treatment.

  • Poorer baseline FA associated with better improvements. No change in White matter following
treatment.
Physical health interventions & Cognition in SZ

• Several studies report cognitive benefits associated with exercise.
  • Exercise associated with improved cognition (Malchow et al 2015)
  • Exercise improved response to CRT (Neuchterlein et al. 2016)
  • Undertaking CRT also associated with increased exercise! (Amado et al 2020)

• Takahashi et al (2020): Re-analysis of earlier study in Malchow 2016 (n=21 SZ versus n=23 controls)
  • The schizophrenia aerobic exercise group showed a significant increase of cortical thickness in the right entorhinal cortex at week 6, becoming n.s. at week 12.
Discussion

• Training effects suggesting a ‘normalisation’ of cortical activity following training (increased activity).

• Lack of statistically significant overlap in regions.
  ➔ reflects different CT approaches.
  ➔ reflects small n sizes.

• Effect size of neural effects associated with CRT unknown
  ➔ Extent of file-drawer problem also unknown.
  ➔ Current literature likely over-estimates neural effects of CRT.
Conclusions: What we know, and don’t know...

1. CRT improvements has been reliably associated with altered brain activation, and to some extent brain structure although the size of this association remains uncertain.

2. Poorer baseline MRI measures are associated with better outcomes (like as in behavioural studies)

3. We can’t say for sure if there are specific brain regions involved, although the pre-frontal regions are often implicated (like CBT).

4. These changes mediate the effects of CRT on cognition and functional outcomes. Precisely how remains unclear.
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