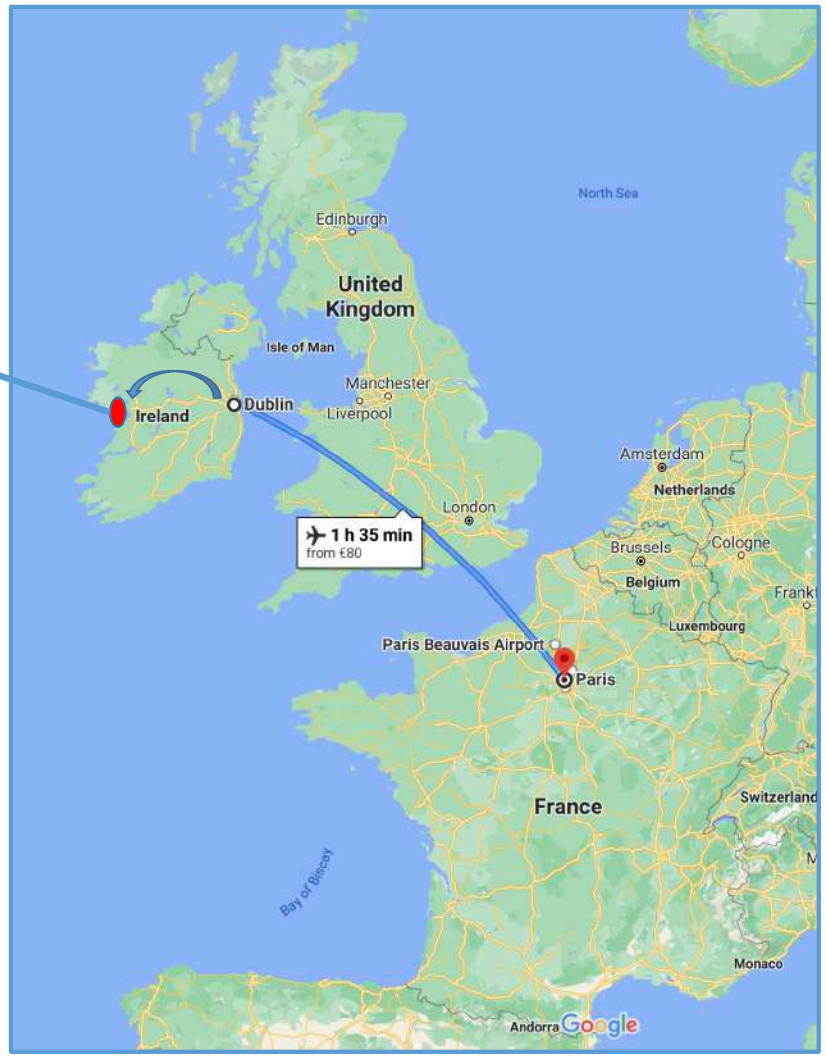
Neural Effects of Cognitive Remediation

Prof. Gary Donohoe
School of Psychology & NICOG, NUI Galway

12ème colloque de l'AFRC, Amphithéâtre Laroque,
Ministère des Solidarités et de la Santé,
Paris - 25 septembre 2020



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

Les lacs de connemara
Michel Sardou

Disclosures

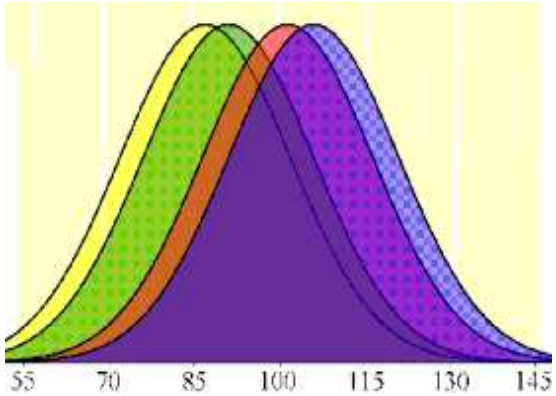
This work is funded by:

No conflicts of interests to report.

Outline

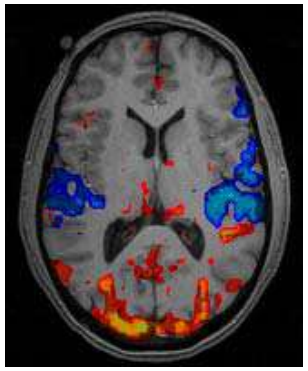
Neural effects of Cognitive remediation

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?

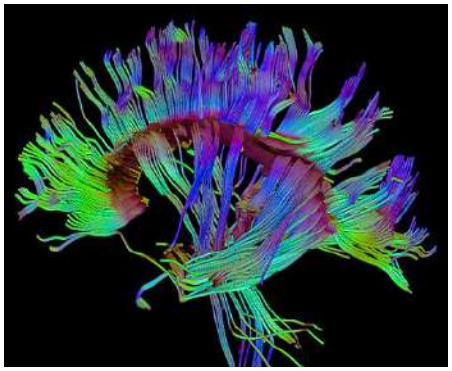


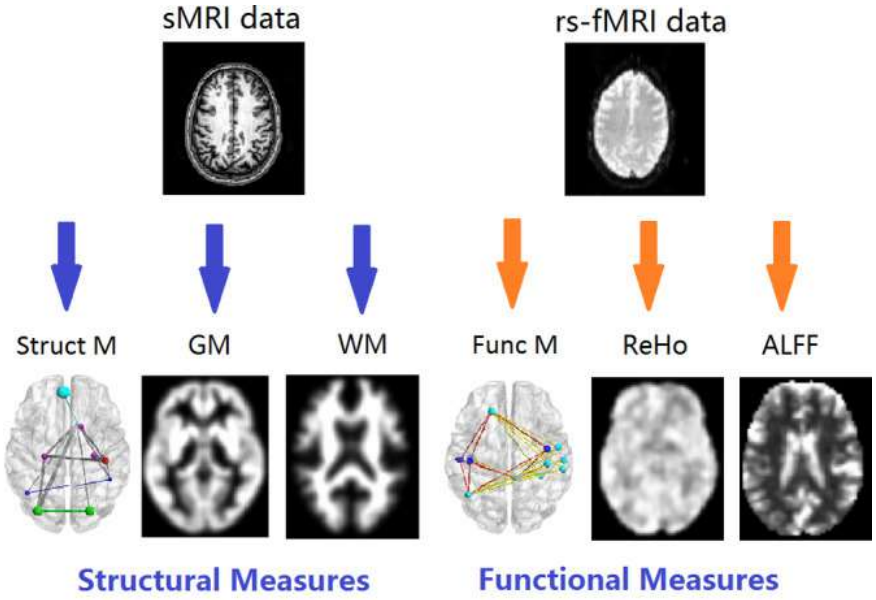
Structural MRI

Functional MRI



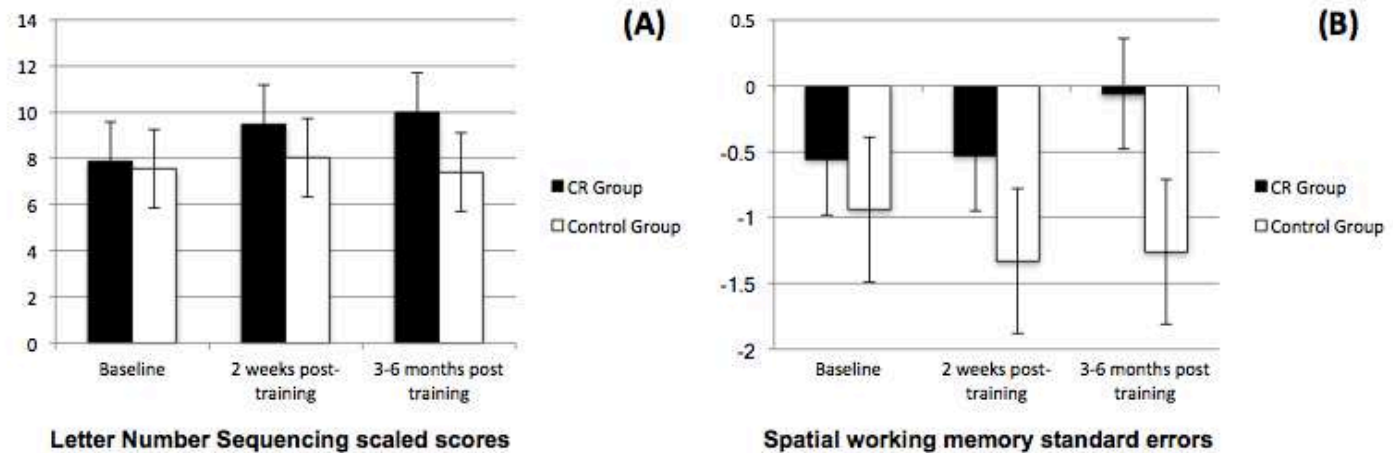
White matter diffusion tensor imaging (DTI)



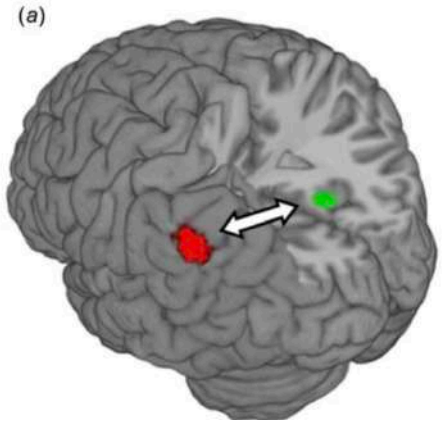


Neuropsychological effects

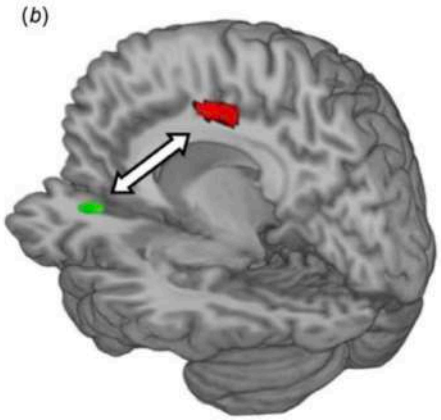
Donohoe et al., (2018)
Psychological Medicine



Functional connectivity effects

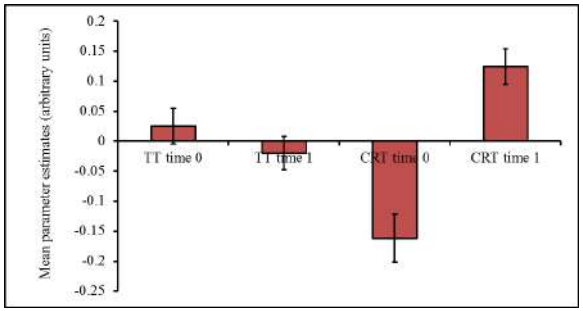


Functional connectivity between the R precuneus (seed region in green) & the L inferior parietal lobule

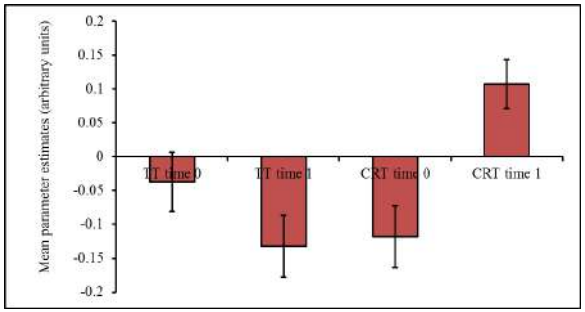


Functional connectivity between the L anterior cingulate cortex (seed region in green) & the R midcingulate cortex.

(a)



(b)



Increased connectivity post intervention

Donohoe et al., Psychological Medicine (2018)

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.

Study rationale

- 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.

Mothersill & Donohoe 2019

Biological Psychiatry: CNNI

Archival Report

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

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

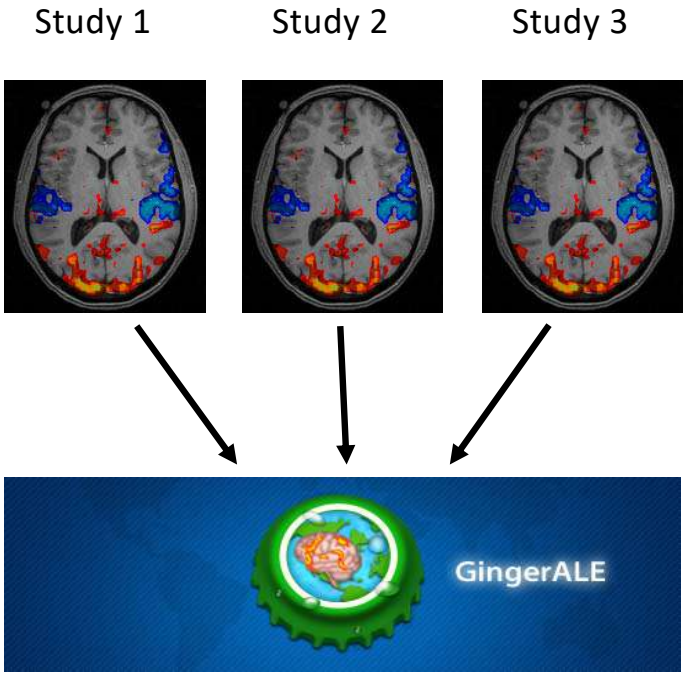
https://doi.org/10.1016/j.bpsc.2019.03.005

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?***

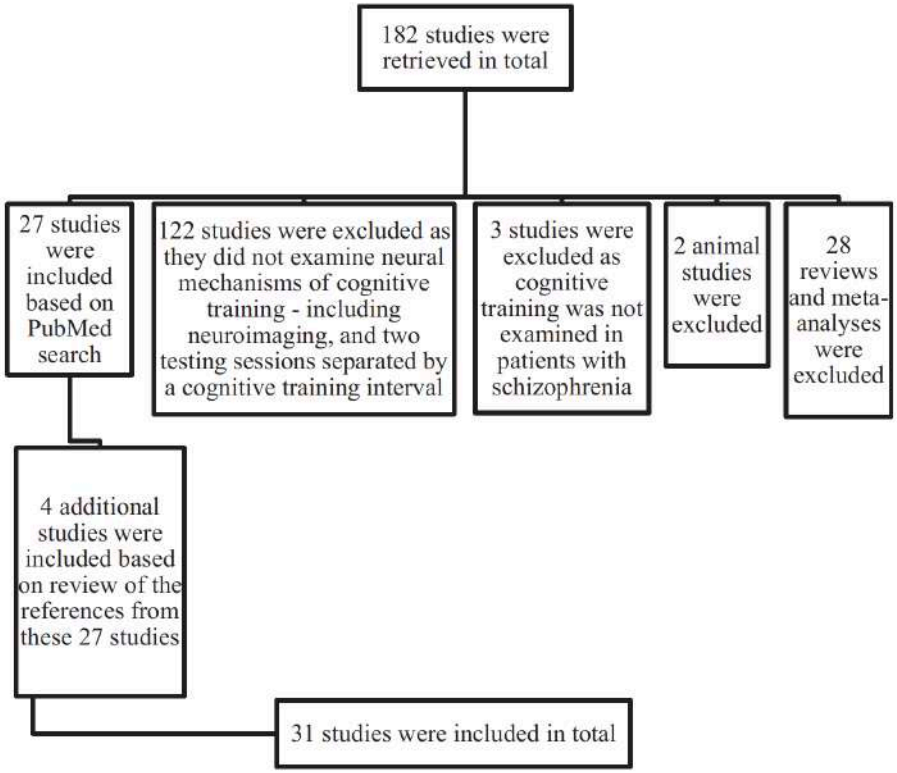


Eickhoff et al. (2017): Hum Brain Mapp 38:7–11.

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).

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

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.

First Author and Year (Reference)	*N*	Cognitive Process(es) Targeted	Weeks
Wykes, 2002 (22)	18	Executive function	12
Haut, 2010 (32)	27	Executive function and memory	4–6
Rowland, 2010 (43)	34	Relational memory	<1
Edwards, 2010 (33)	36	Executive function	<1
Habel, 2010 (34)	30	Social cognition	6
Bor, 2011 (62)	32	Executive function	7
Subramaniam, 2012 (35)	25	Auditory processing, visual processing, and social cognition	16
Hooker, 2012[a] (36)	22	Auditory-based cognition and social cognition	10
Hooker, 2013[a] (37)	22	Auditory-based cognition and social cognition	10
Vianin, 2014 (63)	16	Executive function	14
Subramaniam, 2014 (27)	40	Auditory/visual processing and social cognition	16
Keshavan, 2017 (26)	41	Executive function, memory, and social cognition	>104
Ramsay, 2017 (38)	26	Executive function	16
Guimond, 2018 (41)	15	Semantic association memory	2

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 2nd 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** pariental 3rd most frequently observed (4 peaks).

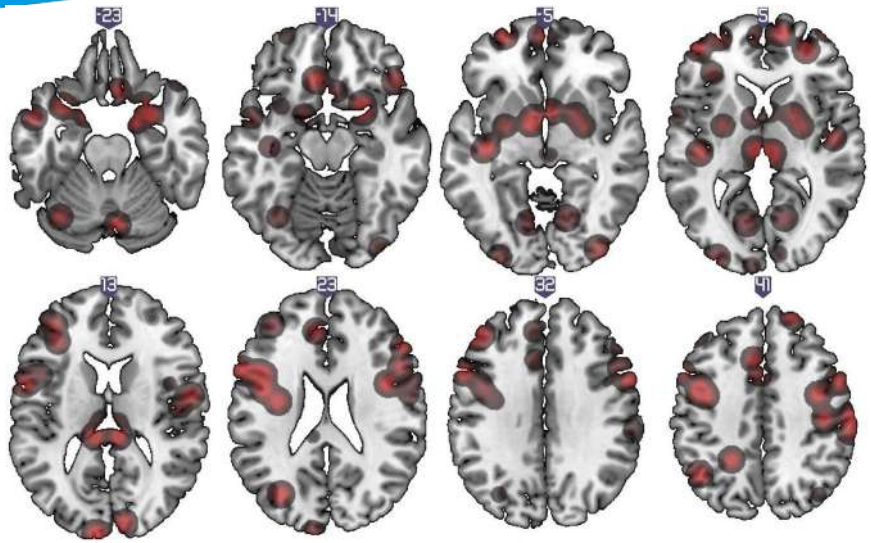
Activation peak = Brain region where brain activation is maximal.

Results: ALE Meta-analysis

- No specific brain regions showing consistent effects.

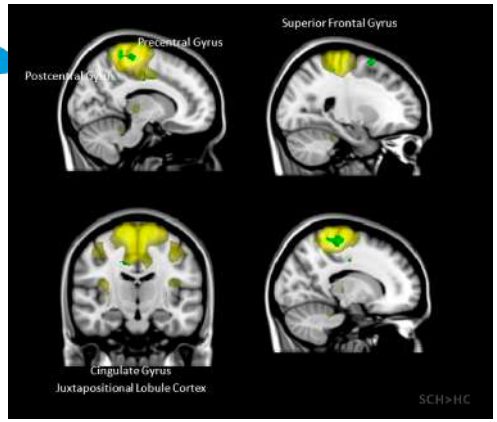
→no clusters showed overlap between two or more studies.

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



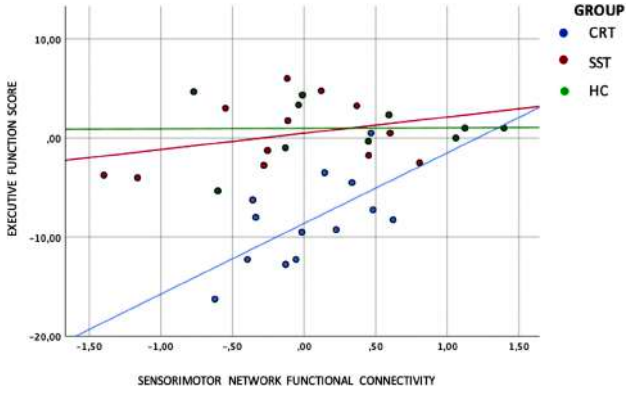
Coordinates of maxima from clusters showing effects of cognitive training across 14 fMRI studies overlaid onto a standard brain template.

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.



- Li et al (2019): WM training associated with increase activity in right insula (n=15v11).

- Mothersill et al (2018): WM training not associated with cortical activity changes relevant to social cognition (n=15v15).

Longitudinal effects of CRT on brain structure

Several studies by Eack and colleagues relevant (Eack et al 2010, Eack et al 2016, Keshevan et al 2020).

- 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.

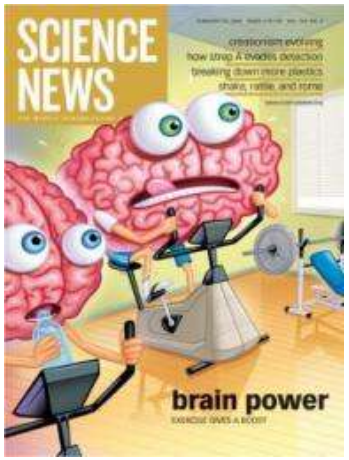
- Eack et al 2016, Keshevan et al 2020 (n=25v16): At 2yr follow up, CT associated with increased BOLD activity in the right dorsolateral prefrontal cortex (DLPFC) and anterior cingulate, and reduced connectivity between these regions. This was in turn associated with improved cognition.

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.
- McClure et al (2019): [N=10]
  - Poorer baseline FA associated with better improvements. No change in White matter following treatment.

Physical health interventions & Cognition in SZ

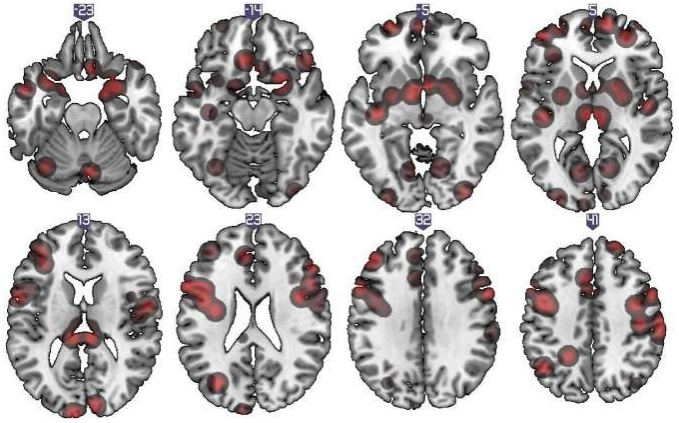


- Several studies report cognitive benefits associated with exercise.
  - Exercise associated with improved cognition (Malchow et al 2015)
  - Exercise improved response to CRT (Neuchterlein et al. 2016)
  - Undertaking CRT also associated with increased exercise! (Amado et al 2020)

- 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.

Acknowledgements:

NICOG, NUI Galway

David O. Mothersill

Rachael Dillon

April Hargreaves

Megan Cowman

Brian Hallahan

Colm McDonald

Emma Frawley

King's College London

Til Wykes

Mateo Cella

McGill University

Martin Lepage

University of Sussex

David Fowler

Clio Berry

Queen's University, Kingston

Chris Bowie

Trinity College Dublin

Marco Castorino

Brian Fitzmaurice

Ian Robertson