



## **Computerised working memory#based cognitive remediation therapy does not affect Reading the Mind in The Eyes test performance or neural activity during a Facial Emotion Recognition test in psychosis**

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## Abstract

Working memory based cognitive remediation therapy (CT) for psychosis has recently been associated with broad improvements in performance on untrained tasks measuring working memory, episodic memory and IQ, and changes in associated brain regions. However, it is unclear if these improvements transfer to the domain of social cognition and neural activity related to performance on social cognitive tasks. We examined performance on the Reading the Mind in the Eyes test (Eyes test) in a large sample of participants with psychosis who underwent working memory based CT (N = 43) compared to a Control Group of participants with psychosis (N = 35). In a subset of this sample, we used functional magnetic resonance imaging (fMRI) to examine changes in neural activity during a facial emotion recognition task in participants who underwent CT (N = 15) compared to a Control Group (N = 15). No significant effects of CT were observed on Eyes test performance or on neural activity during facial emotion recognition, either at  $p < 0.05$  family-wise error, or at a  $p < 0.001$  uncorrected threshold, within a priori social cognitive regions of interest. This study suggests that working memory based CT does not significantly impact an aspect of social cognition which was measured behaviourally and neurally. It provides further evidence that deficits in the ability to decode mental state from facial expressions are dissociable from working memory deficits, and suggests that future CT programs should target social cognition in addition to working memory for the purposes of further enhancing social function.

## **Introduction.**

An important feature of psychosis spectrum disorders is cognitive deficits that predict social and functional disability (Green et al., 2016; Wykes & Reeder, 2005). These include deficits in neurocognitive abilities such as new learning, working memory or reasoning (Schaefer et al., 2013) and social cognitive abilities such as recognising the emotional content of faces (Li et al., 2010), and theory of mind, the ability to attribute thoughts and intentions to other people (Bora et al., 2009). In schizophrenia, deficits in facial emotion recognition and theory of mind are among the strongest predictors of functional outcomes in employment, relationships and independent living (Couture et al., 2006). For example, theory of mind ability predicts between 15% and 50% of variation in outcome measures such as social functioning (Roncone et al., 2002, Brune et al., 2007). In relation to neurocognitive predictors of functioning, verbal memory has been found to be the strongest predictor of functioning outcome (Lepage et al., 2014).

Given that antipsychotic medications do not significantly improve cognitive function (Kucharska-Pietura and Mortimer, 2013), much current research is focussed on psychological interventions such as cognitive remediation therapy (CT), which targets difficulties with cognitive skills such as working memory and social cognition over a period of weeks (Wykes et al., 2011). In an important meta-analysis of CT that included over 2,000 participants, Wykes et al. (2011), reported evidence that CT leads to moderate cognitive improvements (Cohen's  $d = 0.45$ ).

We recently developed a computerised CT program for psychosis targeting working memory (Hargreaves et al., 2015), which was associated with improvements across a range of

cognitive functions including working memory, episodic memory, and performance intelligence quotient (IQ), as well as improvements in social functioning and increased resting-state functional brain connectivity across frontal and parietal regions, assessed using functional magnetic resonance imaging (fMRI; Donohoe et al., 2017). In doing so, our findings supported evidence from working memory training programmes in other populations where training was associated with a transfer of benefits to other cognitive domains, included greater efficiency of stimulus processing and increased attention capacity (Jaeggi et al., 2008; Jaeggi et al., 2010; Kundu et al., 2013; Lilienthal et al., 2013; Rudebeck et al., 2012; Salminen et al., 2012).

Although focussed on working memory, important social and emotional elements were present in our CT program. For example, the program including repeated exposure to facial stimuli: the Faces Snap training task required patients to carefully watch a series of photographs of human faces and press a button when two appeared in a row, and the Focus Faces training task required patients to remember the last two from a series of faces (Hargreaves et al., 2015). Although the training purpose of these tasks was not on emotion recognition, given that some of the facial stimuli presented emotional expressions (e.g. smiling), it is likely that the stimuli used engaged affect recognition processes. Furthermore, even neutral faces can be perceived as emotionally salient due to their structural properties (e.g. high or low eyebrows) and presentation context (e.g. whether an emotional face preceded a neutral face in the task) (Ille et al., 2011; Adams et al, 2012; Wieser and Brosch, 2012), particularly in patients with schizophrenia (Mothersill et al, 2014b).

While neurocognition (e.g. working memory) and social cognition, both affected in schizophrenia, are generally considered to be separate domains (Sergi et al., 2007; Fett et al., 2011), several structural equation modelling studies have examined the relationship between these domains (Vauth et al., 2004; Sergi et al., 2007; Schmidt et al., 2011) and reported medium to large correlations between neurocognitive and social cognitive ability in schizophrenia, suggesting significant overlap. Social cognition is an important predictor of social function in schizophrenia (Vauth et al., 2004; Sergi et al., 2007; Fett et al., 2011), and may act as a mediator between neurocognitive ability and real world social functioning (Brekke et al., 2005; McGlade 2008; Schmidt et al., 2011). In terms of working memory specifically, significant associations with facial emotion recognition ability ( $r = 0.41 - 0.47$ ) have also been reported (Bryson et al., 1997; Bozikas et al., 2004).

Consistent with these findings, CT interventions targeting neurocognition have been reported to also impact social cognition. Gaudelus et al. (2016) reported that CT focused on selective attention led to significant improvements in facial affect recognition, while Corrigan et al. (1995) found that training in other cognitive domains, including verbal memory and vigilance, lead to improved social perception. In terms of working memory training specifically, Schweizer et al. (2013) reported that working memory training based on social and emotional stimuli leads to working memory improvements that resulted in benefits to emotion regulation, a cognitive ability that significantly impacts upon social cognition (Gross, 2002). Similarly, fMRI-based studies further suggest that working memory-based cognitive training impacts upon networks important for social cognition, including the default mode network, which plays a role in theory of mind (Penades et al., 2013) and the affective network, which plays a role in emotion processing (Donohoe et al., 2017). Supporting these findings, fMRI studies of CT programs in schizophrenia most commonly report increased

neural activity after training within the prefrontal cortex, a brain region that shows reduced activity in schizophrenia, and plays an important role in social cognition (Penades et al., 2017). For example, individuals with prefrontal lesions perform more poorly on tests of mental state decoding from viewed facial expressions (Dal Monte et al., 2014). Similarly, in healthy volunteers, sub regions of the prefrontal cortex are activated by mental state decoding tests (Mothersill et al., 2014a; Adams et al., 2009).

Based on the evidence above suggesting overlap between cognitive and social cognitive processes, together with evidence that various forms of CT are associated with significant benefits in social function (Wykes et al, 2011), one important question is whether CT targeting working memory impacts on cognitive and neural processes related to social cognition. Given the evidence reviewed above, to address the question of whether cognitive benefits following working memory CT program would generalise to social cognition at behavioural and cortical levels, we tested three related hypotheses: (a)

*that working memory-based CT would lead to improvements in mental state decoding ability, (b) that working memory-based CT would lead to altered neural activity during facial emotion recognition, and (c) that working memory-based CT would lead to increased improvements in mental state decoding ability in those participants who showed the greatest working memory improvement after training compared to participants showing less or no working memory improvement.*

## **Materials and methods.**

### **Study participants.**



The first group involved in this study participated in a pilot study, in which we examined the feasibility of an 8-week working memory CT program (Hargreaves et al., 2015) (N = 38, 18 participants who completed CT and 20 participants who were assigned to the Control Group). The second group participated in a randomised controlled trial (RCT) of the same 8-week working memory CT program in order to investigate the effectiveness of this program in treating cognitive deficits in psychosis (Donohoe et al., 2017) (N =52, 25 CT participants and 27 Control Group participants). Combining these samples allowed us to examine performance on the Reading the Mind in the Eyes (Eyes test) in a larger sample (N = 90), i.e. 43 CT participants and 47 Control Group participants (Dillon et al., 2016; Donohoe et al., 2017; Hargreaves et al., 2015). The Eyes test is an established measure of mental state decoding in which participants must determine what a person is thinking from a black and white photograph of the eye region of the face (Baron-Cohen et al., 2001).

All participants included in the current pooled analysis (N = 90) were only the participants who successfully completed CT training (or Control), and neuropsychological testing (Eyes test) before and after CT training (or Control). This is a subset of a larger group of participants who were originally enrolled in the study and were randomised to CT or Control Groups, but either did not complete all of these parts of the study, or dropped out.

fMRI analysis of the facial emotion recognition task consisted of a subset of 30 participants with psychosis from our RCT, i.e. 15 CT participants and 15 Control Group participants (Donohoe et al., 2017). fMRI participants were selected if they consented to participate in this add-on assessment and met additional MRI-specific inclusion criteria (e.g. no pacemaker or certain metal implants, no history of claustrophobia).

Participant diagnosis was confirmed by a trained psychiatric nurse based on a Structured Clinical Interview for DSM-IV (SCID), interview, review of family and staff reports and chart review. Patients with affective disorders and those without affective disorders were diagnosed in the same way, i.e. SCID interview confirmed that both sets of patients had a history of psychotic symptoms. Inclusion criteria were: 18 to 65 years, a diagnosed psychotic disorder, community based and clinically stable, engaged in some activity and could provide informed consent in accordance with the local ethics committees (The St. James's Hospital Dublin / Adelaide and Meath Hospital Dublin Research Ethics Committee; The Newcastle Hospital Ethics Committee; Galway University Hospitals Clinical Research Ethics Committee). We can confirm that full ethical approval for our study was granted by each of the above committees. Exclusion criteria were that participants had no history of organic impairment, head injury resulting in a loss of consciousness, or drug abuse within the preceding 3 months.

All experiments were undertaken with the understanding and written consent of each participant, and the study conforms to the World Medical Association Declaration of Helsinki.

### **Intervention.**

CT programme:

This study used an online CT programme that specifically targets working memory and was developed by our group (Dillon et al., 2016; Donohoe et al., 2017; Hargreaves et al., 2015;

McAvinue et al., 2013). The programme consisted of education on working memory, strategy-based learning and practice of nine working memory training exercises. CT participants were required to complete 30 to 40 minutes of training per day for five days a week. They met with the study therapist for 45 minutes once per week for the 8 weeks. The CT programme is described in full in Donohoe et al., 2017.

During the pilot study, weekly contact with the study therapist differed from the RCT and occurred over the phone. However, the online, computerised CT program was identical across both the pilot study and the RCT.

Control Group:

During the RCT, participants in the Control Group met weekly with the same CT therapist as the CT group and for the same amount of time (about 45 minutes in both groups).

Participants were encouraged to chat about topics of their choice in an open ended conversation with the therapist, including topics such as the participants' previous week's events to their hobbies and current affairs. Symptoms were not directly discussed and there was no specific agenda for each meeting. The therapist aimed to take a nondirective and empathic approach. Overall, the Control Group was designed to mirror the amount of time participants spent with the therapist in the CT group.

During the pilot study, Control Group treatment differed from the RCT and consisted of treatment as usual, including regular medical review, general psychosocial support from a community psychiatric nurse, and additional inputs from occupational therapy and social

work (Hargreaves et al., 2015). Treatment as usual also occurred for all other interventional conditions.

### **Measures and Procedure:**

43 CT and 47 Control Group participants included in the present study underwent neuropsychological testing before and after the 8-week intervention. A subset also underwent MRI scanning before and after the intervention.

The primary outcome measure of this study was Eyes test score. In our previous study, we demonstrated that CT did not change Eyes test performance (Donohoe et al., 2017). In order to carry out more sophisticated analysis, we increased the sample to 90 participants.

Other measures included the schedule for the assessment of positive symptoms and the schedule for the assessment of negative symptoms (SAPS and SANS) (Andreasen, 1984; Andreasen, 1983), anti-psychotic medication, demographic information and IQ. IQ was measured from the Similarities (a measure of verbal IQ) and Matrix Reasoning (a measure of performance IQ) subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Full-scale IQ was estimated based on published norms for the 2 subtest version of this test (Donohoe et al., 2017). Anti-psychotic medication was recorded at the start of the study, and overall anti-psychotic medication data for each participant was converted to chlorpromazine equivalent in m.g./day.

The procedure of this study was as follows: All participants (N = 90) completed the Eyes test with a research psychologist before, and after, the 8-week working memory CT program (or Control Group treatment), as part of a larger neuropsychological test battery (described in full in Hargreaves et al., 2015 and Donohoe et al., 2017).

### **Statistical analysis.**

IBM SPSS Statistics Version 23.0.0.0 was used for all demographic and behavioural data analysis. Age and baseline IQ were compared between CT and Control Group using an independent t test, and gender was compared between CT and Control Group using a Pearson's chi-squared test. We also examined possible differences in clinical information between groups – anti-psychotic medication (chlorpromazine equivalent in m.g./day), schedule for the assessment of positive symptoms (SAPS) and schedule for the assessment of negative symptoms (SANS).

Consistent with our previous study (Donohoe et al., 2017), we examined effects of CT on Eyes performance using Analysis of Covariance (ANCOVA). In this analysis, performance on the Eyes test (raw Eyes score) was designated as the dependent variable, group (CT versus Control Group) was designated as the independent variable, and baseline Eyes performance, age, baseline IQ and gender were entered as covariates. Gender was included as a covariate in this analysis due to the reported effects of gender on Eyes test performance (Kirkland et al., 2013).

Next, we examined whether CT effects on Eyes performance was greater in participants who showed greater neurocognitive improvements following treatment. We examined

performance on the letter number sequencing test (LNS) from the Wechsler Memory Scale, 3rd edition (Wechsler, 1998), a measure of working memory, as CT treatment had the largest effect on performance of this test in our RCT (Donohoe et al., 2017). We subtracted baseline LNS raw score from 0-2 weeks post-intervention LNS raw score, to get a measure of LNS change (N = 77 participants with LNS data at baseline and 0-2 weeks post-intervention). We then repeated our ANCOVA (described above) separately for two groups – those with the highest positive LNS change (N = 39), and those with lower or negative LNS change (N = 38). To define high and low scores, we arranged LNS change scores in SPSS in order of magnitude, and then allocated the highest 39 scores to “highest positive LNS change” and allocated the lowest 38 scores to “lower or negative LNS change.”

Given that our sample of 90 participants consisted of data from our pilot CT study (N = 38) and our RCT (N = 52), and given small methodological differences between the two studies (e.g. a weekly telephone call with a therapist in the CT group in the pilot study, versus a face to face meeting in the RCT), we re-ran our ANCOVA analysis with pilot or RCT included as an additional covariate. However, results remained non-significant, thus, it is unlikely that methodological differences between pilot and RCT studies affected results, especially considering that both studies were the same in terms of the computerised CT program itself, the duration of treatment (8 weeks), and the amount of therapist contact.

### **MRI methods.**

Participants performed a facial emotion recognition test in which they watched a series of black-and-white videos of actors displaying neutral or angry facial expressions (Grosbras and Paus, 2006). A non-facial baseline condition consisted of videos of black and white circles

expanding and then contracting. Participants also performed a face recognition task at the end of the scan, to examine their attention to the faces during the scan itself. All participants scored  $> 3/5$  correct at both time points, except one participant, who scored  $< 3$  on their first scan.

MRI data were acquired on a 3T Philips Achieva MR system (Philips Medical Systems, Best, The Netherlands), which was equipped with a gradient strength of 80 mT/m and a slew rate 200 T/m/s, using an 8-channel receive-only head coil, in the Centre for Advanced Medical Imaging (CAMI) at St. James's Hospital, Dublin, Ireland. A 3D Inversion Recovery prepared Spoiled Gradient Recalled echo sequence was used to obtain T1-weighted images of the brain (for more precise normalisation of the functional images to a standard template), with a FOV =  $256 \times 256 \times 160 \text{ mm}^3$ , a spatial resolution of  $1 \text{ mm}^3$ , TR/TE = 8.5/3.9 ms, TI = 1060 ms, flip angle =  $8^\circ$ , SENSE factor = 1.5, acquisition time = 7 min 30 s.

Facial emotion recognition fMRI data were acquired using a SE-EPI sequence which included a dynamic scan time of 2 s, with a FOV =  $240 \times 240 \times 132 \text{ mm}$ , spatial resolution =  $3 \times 3 \times 3.2 \text{ mm}$ , 38 slices with interslice gap = 0.3 mm, TR/TE = 2000 / 28 ms, SENSE factor = 2, with SPIR fat suppression and dynamic stabilisation. In total, 174 dynamic scans were acquired for the facial emotion recognition task in an acquisition time of 5 min 48 s.

Spatial pre-processing was carried out using Statistical Parametric Mapping (SPM8, v6313, <http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) (Ashburner et al., 2012) and MATLAB R2014a (v8.3.0.532; <http://www.mathworks.co.uk/>). Functional images were first realigned to the mean image to reduce the effects of motion. Next, the T1 structural image was co-

registered to the mean functional image for more precise spatial normalisation. The realigned functional images were then normalised to MNI (Montreal Neurological Institute) space using unified segmentation with a voxel size of  $2 \times 2 \times 2 \text{ mm}^3$  (Ashburner and Friston, 2005) and smoothed with an 8 mm FWHM (full width at half maximum) isotropic Gaussian filter. We performed artefact detection using the Artefact Detection Tools (ART) toolbox ([http://www.nitrc.org/projects/artifact\\_detect/](http://www.nitrc.org/projects/artifact_detect/)). Pre-processed images that showed variations in global mean intensity  $> 3$  standard deviations, and/or composite motion  $> 1 \text{ mm}$ , were considered outliers (Whitfield-Gabrieli, S., personal correspondence) and entered as covariates in each individual's first level model.

Statistical analysis was performed using a general linear model (GLM) approach (Friston et al., 1994) and the following four contrasts that we have used previously (Mothersill et al., 2014b):

1. All faces (angry and neutral) versus baseline
2. Angry faces versus neutral faces
3. Angry faces versus baseline
4. Neutral faces versus baseline

Contrast maps were entered into a random effects analysis to examine group x time interactions – a flexible factorial model in SPM8 with factors subject (variance set to equal, independence set to yes), group (variance set to unequal, independence set to yes) and time (variance set to equal, independence set to no) (Gläscher and Gitelman, 2008). Statistical significance was set at  $p < 0.001$  (uncorrected) and clusters were considered statistically significant at a  $p < 0.05$ , family-wise error (FWE) corrected for multiple comparisons across



the whole brain at the cluster level. Given that we have previously reported differences in Blood Oxygenation Level Dependent signal (BOLD) between schizophrenia spectrum participants and healthy controls during this task across three clusters (Mothersill et al., 2014b), we used maps of these clusters as three regions of interest (ROIs) in three further ROI analyses (**Table 1**).

>> Table 1 <<

### **Power analysis.**

To investigate the magnitude of effect we would be able to detect with our sample, we performed a sensitivity power analysis using G\*Power 3.1.9.2 (Faul et al., 2009; Faul et al., 2007). Using an ANCOVA as an example, with a sample size of 78 (the final sample used in the 0-2 week post intervention analysis, see Results),  $p$  set to 0.05, numerator degrees of freedom set to 1, two groups, and 4 covariates, we would have 80% power to detect effects of Cohen's  $f = 0.32$ . This is equal to a Cohen's  $d$  of 0.64 and is considered a medium effect (Cohen's  $f$  to Cohen's  $d$  conversion performed using:

[https://www.psychometrica.de/effect\\_size.html](https://www.psychometrica.de/effect_size.html)). Thus, our current sample is powered to detect medium to large effects of CT on Eyes performance, but underpowered to detect small effects. We also performed an ANCOVA in a smaller sample of participants with highest, and then lowest change in LNS score ( $N = 38$  in the smallest group). Using the same ANCOVA model, we would have 80% power to detect effects of Cohen's  $f = 0.47$ , equal to a Cohen's  $d$  of 0.94, i.e. a large effect.

For the fMRI sample, using a repeated measures ANOVA as an example, with a sample size of 30 and  $p$  set to 0.001 (our exploratory statistical threshold in our ROI analysis), we would have 80% power to detect effects of Cohen's  $f = 0.42$ . This is equal to a Cohen's  $d$  of 0.84 and is considered a medium effect. Thus, our current fMRI sample is powered to detect medium CT group  $\times$  time effects on BOLD response at the uncorrected statistical threshold used, but underpowered to detect smaller effects at this threshold.

## **Results and Statistical Analyses.**

### **Behavioural results.**

Neuropsychological analysis participant demographics are described in **Table 2**. We first examined age and baseline IQ variables to see if there were any outliers, observations different from the majority. It is important to be able to detect and examine these outliers as these do not fit a model well and may result from experimental error (Rousseeuw and Hubert, 2011). We defined outliers as any value more than 1.5 times the interquartile range of the values, a standard method of outlier detection (Rousseeuw and Hubert, 2011). This revealed that there were two baseline IQ outliers. Overall, there was a significant difference in age regardless of including or excluding these two outliers. There was a trend level difference in baseline IQ only when these two outliers were removed (see **Table 2**). Given that there was a trend level difference in baseline IQ with these two outliers removed, we excluded these cases and included baseline IQ as an additional covariate in further analysis. The total number of individuals entered into the post-treatment analysis was therefore 78 (10 Control Group participants were missing baseline IQ data, and two baseline IQ outliers were removed).

Further inspection of Eyes performance outliers at baseline and at 0-2 weeks post-intervention identified three outliers, defined as any score more than 1.5 times the interquartile range of the scores (Rousseeuw and Hubert, 2011). The ANCOVA was re-run with these outliers removed, but revealed similar results. As the analysis was not significantly affected by including or excluding these three outliers, our final results include them.

No significant differences were observed between the CT and Control Group for clinical variables – anti-psychotic medication (chlorpromazine equivalent in m.g./day), schedule for the assessment of positive symptoms (SAPS) and schedule for the assessment of negative symptoms (SANS) (all  $p > 0.05$ , see **Table 2**).

>>Table 2<<

No significant effects of CT group were observed on Eyes performance at 0-2 weeks post CT treatment (see **Table 3**). Similarly, to determine whether effects on social cognition were more apparent in individuals who showed greatest gains in working memory post training (based on LNS performance), a median split of the sample was performed and those in the top half of the split were analysed separately; the results remained non-significant ( $p = 0.136$ ) (see **Table 3**).

Given that the 38 participants with lower or negative LNS test change showed consistently higher Eyes scores 0-2 weeks post-intervention, we compared baseline LNS and Eyes performance between LNS test change groups using an ANCOVA, to examine whether the higher LNS test change group were more impaired so had more scope for improvement (see **Table 4**). This revealed a significant difference in baseline LNS score between LNS test change

groups, i.e. the group showing the greatest LNS improvement also showed the lowest LNS score at baseline. However, groups did not differ on Eyes performance.

>> Table 3 <<

>>Table 4<<

Finally, in order to examine the effects of CT group on Eyes performance in our whole sample of 90 participants, we repeated each ANCOVA without excluding outliers and excluding age, gender or baseline IQ as covariates. Again, no effects of working memory training on social cognition were observed.

### **fMRI Participant demographics.**

We first examined possible differences in age, gender, baseline IQ and ART outliers between CT and Control Group. No significant differences were observed between the CT and Control Group for age, gender, or baseline IQ (all  $p > 0.05$ , see **Table 5**). There were no significant time x group interactions observed on number of ART outliers estimated for the Faces task across time 0 and time 1, across CT and Control Group ( $p > 0.05$ , see **Table 5**). Examination of age, baseline IQ and ART outlier variables revealed that there were a small number of outliers (1 baseline outlier, 8 ART outlier score outliers). As such, statistical tests were re-run with these outliers removed. Given that no significant differences emerged regardless of whether outliers were removed or not, we included these cases in the statistical examination of fMRI participant demographic information.

We also examined possible differences in clinical information between groups – anti-psychotic medication (chlorpromazine equivalent in m.g./day), schedule for the assessment of positive symptoms (SAPS) and schedule for the assessment of negative symptoms (SANS). No significant differences were observed between the CT and Control Group for these variables (all  $p > 0.05$ , see **Table 5**).

>>Table 5<<

### **fMRI results.**

No significant CT group x time interaction effects were observed on BOLD response for any of the contrasts examined, either at the whole brain level or within ROIs. Within each of our ROIs, we also examined CT group x time interaction effects on BOLD response at an exploratory threshold of  $p < 0.001$ , uncorrected, extent threshold 10 voxels, however, no effects were observed.

To present BOLD response in more detail across groups, time points, and ROIs, we performed one-sample t-tests examining overall response at each time point and for each contrast (i.e. 4 one-sample t-tests for timepoint 0 and 4 one-sample t-tests for time point 1), and then plotted mean parameter estimates extracted from ROIs for both groups for each time point and contrast. These are presented in **Figures 1 to 4**.

>>Figure 1<<

>>Figure 2<<

>>Figure 3<<

>>Figure 4<<

### **Discussion.**

This study examined the effects of a working memory based CT program, previously shown to improve general cognitive function and social and occupational function (Hargreaves et al., 2015, Donohoe et al., 2017), on decoding of emotion / mental state from viewed facial expressions at the both behavioural and neural levels, in people diagnosed with psychosis. No significant findings were observed on any of the analyses undertaken, indicating that very limited benefits to emotion / mental state decoding ability accrued, as measured either behaviourally by Eyes task performance, or cortically in terms of facial emotion recognition, following working memory training at either behavioural or cortical levels of analysis. To our knowledge this is the first study to specifically investigate generalisation from working memory-based CT to decoding of emotion / mental state from viewed facial expressions.

### **Dissociation of social deficits from working memory deficits in psychosis.**

Given that a major focus of CT programs generally is to improve social functioning, it is important to determine whether and to what degree this benefit accrues from benefits to social cognition. Social cognition represents a specific domain of deficits in schizophrenia that are predictive of social function. Furthermore, we have previously shown that these deficits mediate the effects of general cognitive ability on social and occupational outcome (McGlade et al., 2006), making treatment of these specific deficits an important priority for enhancing social functioning. Although our CT program was associated with significant improvements in social functioning (Donohoe et al., 2017), these benefits accrued independently of significant improvements on the behavioural or cortical measure employed in this study. As such, they

support the view that deficits in mental state decoding from viewed facial expressions are dissociable from purely working memory deficits in psychosis. This view is supported by studies reporting that performance on other social cognitive tasks is impaired in schizophrenia even when controlling for non-social forms of cognition (Brune, 2005; Sprong et al., 2007).

Our study suggests that the benefits in social functioning associated with gains in working memory, episodic memory and general cognitive performance, occur independently of specific effects on either facial emotion processing or mental state decoding. One reason for this might be that working memory and episodic memory overlap to some extent either in terms of the cognitive demands of the tasks measured, or the cortical networks activated, whereas the Eyes task and facial emotion recognition test used here overlapped less in terms of task demands and cortical demands with those targeted by the working memory training tasks which participants performed, with each independently capable of contributing to improved social functioning.

### **CT, social cognitive training and social function.**

When combined with social cognitive training, CT has previously been associated with increased BOLD response during facial emotion recognition across several brain regions in people diagnosed with schizophrenia, including the bilateral amygdala, right inferior frontal gyrus and right postcentral gyrus (Habel et al., 2010; Hooker et al., 2012; Hooker et al., 2013). The magnitude of these effects is typically large, for example ranging from Cohen's  $d = 1.51$  to  $d = 2.10$  in Hooker et al., 2012 and Hooker et al., 2013. These increases in BOLD response also predict behavioural improvements on social cognitive tasks performed outside the scanner, consistent with a recent meta-analysis by Kurtz and Richardson (2012) which reports small to large positive effects of social cognitive training on facial emotion recognition and theory of mind in schizophrenia, though using different cognitive tests to those used in the present study.

Our study highlights the importance of specifically targeting emotion / mental state decoding ability in future CT programs, as this might be necessary to produce large improvements. This may potentially be achieved by utilising hybrid therapeutic approaches that simultaneously treat neurocognitive and social cognitive contributors to impaired social and occupational functioning.

### **Study Limitations.**

As already noted, although our neuroimaging sample was powered to detect large effects of CT, it was nevertheless underpowered to detect small to moderate effects, especially using stringent FWE-corrected statistical thresholds. Given that CT generally has been associated with moderate effects on behavioural outcomes, it is possible that population effects of CT on neural activity are smaller in magnitude than previously reported, and overestimated by current studies, consistent with other areas of neuroscience in which small studies typically inflate the magnitude of the effect observed (Button et al., 2013). As such, it is recommended that future studies examine the effects of CT on neural response in larger samples to increase statistical power to detect smaller effects. However, notwithstanding this, we note that changes in cortical activation during Resting State were detectable following this training in our original study (Donohoe et al., 2017) and that it was specifically a cortical change in social cognition that was not observed here.

As previously mentioned, two of our working memory training tasks specifically used social stimuli (Faces Snap and Focus Faces). Although performance data were unavailable for all participants for these tasks, examining this data and how it might relate to later performance on social tasks after training would be a valuable addition to future studies examining effects of CT programs on social cognition in order to examine whether the proximal relationship



between the training stimuli and the measured task stimuli determines the amount of improvement observed.

Only some aspects of social cognition – specifically, the ability to decode emotion / mental state from viewed facial expressions – were assessed in this study. Other facets of social cognition that may require, and hence be more sensitive to changes in, working memory include the The Awareness of Social Inference Test (TASIT) (Green et al., 2012), which requires participants to view social scenes to identify if a person is lying or demonstrating sarcasm. Our CT program improved social functioning without improving mental state decoding ability, suggesting that the facets of social cognition and / or tests examined in this study may not be the most important for, or predictive of, successful social or community functioning. For each of these reasons, future studies should examine effects of working memory based CT on other facets of social cognition using other social cognitive tests.

When we examined social cognition effects in participants who showed the largest working memory gains, the results remained non-significant, but the effect size increased from  $d = 0.18$  to  $d = 0.56$ , and the  $p$  value was reduced from 0.45 to 0.136. Although this may imply an effect of CT on Eyes score, these results are limited by the imbalance of CT and Control Group participants in this subgroup of 39 participants (28 CT versus 11 Control). Similarly, the smaller sample of 39 participants with the largest gains was only powered to detect large effects (see Materials and methods section). As such, further examination in larger and more balanced samples is warranted.

Overall, while our sample was not powered to allow us to discount the possibility that small benefits to emotion / mental state decoding ability accrued from our working memory training,

we can conclude that social cognitive benefits, as least using the measures employed in this study, did not accrue from a training program focused on working memory training. This is consistent with a study by Fisher et al. (2009), who reported no effects of an auditory training program that heavily engaged working memory on social cognition in schizophrenia (N = 55). Finally, while the Schweizer et al. (2013) study did observe benefits to emotional regulation following working memory training, as noted, this training program (based on healthy participants only) specifically targeted social and emotional stimuli in their working memory training program. Further, they then measured its effects on emotion regulation rather than either emotion recognition or theory of mind – the aspects of cognition typically observed to be impaired in schizophrenia. In our view these differences may account for the divergence in findings observed.

### **Conclusion.**

In conclusion, this study examined effects of a working memory based CT program on the ability to decode emotion / mental state from viewed facial expressions at both behavioural and neural levels in people diagnosed with psychosis, showing no significant effects. These findings provide further evidence that emotion / mental state decoding deficits in psychosis are dissociable from working memory deficits and suggests that future CT programs should specifically target social as well as neurocognitive deficits.

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### **Competing Interests.**

All authors confirm that they have no conflicts of interest in relation to this manuscript.

### **Author Contributions.**

Mothersill undertook statistical and fMRI analysis and wrote the manuscript. Dillon, Hargreaves, Furey and Mothersill collected the data. Corvin, McDonald, Hallahan and Fitzmaurice coordinated patient recruitment to the study. Castorina and Robertson were involved with the development and management of the online computer training programme used in the research. Fagan and Meaney were involved with the development and management of the MRI acquisition protocol. Wykes was an adviser on the study. Donohoe designed the study and wrote the protocol. All of the authors have contributed to the writing and editing of the manuscript and approve its contents.

### **Data Accessibility.**

We are unable to make primary data reported in this manuscript publically available as this is not covered in the original Ethical Approval granted to grant no. 1466. However, we welcome collaboration and use of this data for the purposes of collaborative meta-analyses.

### **Abbreviations.**

ANCOVA = Analysis of Covariance

ART = Artefact Detection Tools

BOLD = Blood Oxygenation Level Dependent signal

CT = cognitive remediation

CT = cognitive remediation therapy

Eyes test = Reading the Mind in the Eyes test

fMRI = functional magnetic resonance imaging

FWE = family-wise error

FWHM = full width at half maximum

GLM = general linear model

LNS = letter number sequencing test

MNI = Montreal Neurological Institute

RCT = Randomised controlled trial

ROI = regions of interest

SANS = schedule for the assessment of negative symptoms

SAPS = schedule for the assessment of positive symptoms

SCID = Structured Clinical Interview for DSM-IV

sd = standard deviation

SPM8 = Statistical Parametric Mapping

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**Table 1: Clusters showing altered activity in schizophrenia compared to healthy controls in Mothersill et al., 2014b, that were subsequently used as regions of interest to examine CT group x time interactions on BOLD response in the present study.**

<b>Cluster peak</b>	<b>Finding in Mothersill et al., 2014b</b>	<b>Contrast examined in ROI<sup>a</sup> analysis in the current study</b>
Right anterior cingulate / BA 24	Decreased reduction in BOLD response during faces (angry and neutral) versus baseline contrast in schizophrenia versus controls	Faces (angry and neutral) versus baseline
Left cerebellum (lobule VII, Crus I)	Increased BOLD response during faces (angry and neutral) versus baseline contrast in controls versus schizophrenia	Faces (angry and neutral) versus baseline
Left medial frontal gyrus / BA 10	Decreased reduction in BOLD response during angry faces versus baseline contrast in schizophrenia versus controls	Angry faces versus baseline

<sup>a</sup>ROI = region of interest

**Table 2: Neuropsychological analysis participant clinical and demographic information**  
(2 baseline IQ outliers removed).

	<b>CT participants (n = 43)<sup>a</sup></b>	<b>Control participants (n = 45)<sup>b</sup></b>	<b>Statistic<sup>c</sup></b>	<b>p value</b>
<b>Mean age in years (s.d.<sup>d</sup>)</b>	41.19 (10.86)	45.96 (10.06)	t = 2.14	0.04
<b>Gender (M:F)</b>	31:12	27:18	$\chi^2 = 1.43$	0.23
<b>Baseline IQ (s.d.)<sup>e</sup></b>	97.07 (16.85)	89.83 (14.92)	t = 1.99	0.05
<b>Mean chlorpromazine equivalent in m.g./day (s.d.)<sup>f</sup></b>	408.11 (429.03)	442.22 (481.46)	t = 0.295	0.769
<b>SAPS<sup>g</sup> Global Rating of Hallucinations (last month) (s.d.)</b>	1.37 (0.88)	1.42 (1.12)	t = 0.20	0.85
<b>SAPS Global Rating of Severity of Delusions (last month) (s.d.)</b>	1.83 (1.34)	1.78 (1.36)	t = 0.14	0.89
<b>SAPS Global Rating of Severity of Bizarre Behaviour (last month) (s.d.)</b>	1.17 (0.45)	1.19 (0.65)	t = 0.16	0.87
<b>SAPS Global Rating of Positive Formal Thought Disorder (last month) (s.d.)</b>	1.31 (0.72)	1.61 (1.15)	t = 1.25	0.22
<b>SANS<sup>h</sup> Global Rating of Affective Flattening (s.d.)</b>	2.09 (1.48)	1.74 (1.18)	t = 1.03	0.31
<b>SANS Global Rating of Inappropriate Affect (s.d.)</b>	1.06 (0.34)	1.07 (0.36)	t = 0.09	0.93

<b>SANS Global Rating of Alogia (s.d.)</b>	1.74 (1.01)	1.42 (0.89)	t = 1.38	0.17
<b>SANS Global Rating of Avolition (s.d.)</b>	1.80 (1.26)	1.58 (0.96)	t = 0.80	0.43
<b>SANS Global Rating of Anhedonia-Asociality (s.d.)</b>	2.00 (1.39)	1.87 (1.02)	t = 0.42	0.67
<b>SANS Global Rating of Attention (s.d.)</b>	1.86 (1.29)	1.48 (0.96)	t = 1.32	0.19

<sup>a</sup>43 CT participants includes participants with the following diagnosis: 23 schizophrenia, 4 schizoaffective disorder, 6 bipolar disorder, 1 major depressive disorder, 9 other psychosis

<sup>b</sup>45 Control Group participants includes participants with the following diagnosis: 30 schizophrenia, 7 schizoaffective disorder, 3 bipolar disorder, 1 major depressive disorder, 4 other psychosis

<sup>c</sup>t statistic derived from an independent t-test between groups;  $\chi^2$  value derived from Pearson's chi-squared test with variables group and gender

<sup>d</sup>s.d. = standard deviation

<sup>e</sup>Baseline IQ data available for 78 out of 88 participants (43 CT participants and 35 Control Group participants)

<sup>f</sup>Chlorpromazine equivalent in m.g./day available for 62 out of 88 participants (33 CT participants and 29 Control Group participants)

<sup>g</sup>Schedule for the assessment of positive symptoms (Andreasen, 1984), available for 35 CT participants and 31 Control Group participants (32 Control participants had Global Rating of Severity of Delusions data, 31 of these Control participants had data for all of the other variables)

<sup>h</sup>Schedule for the assessment of negative symptoms (Andreasen, 1983)

**Table 3: Neuropsychological results for 0-2 weeks post intervention time-point.**

	<b>CT</b>	<b>Control Group</b>	<b>F statistic<sup>a</sup></b>	<b>p value</b>	<b>Effect size (Cohen's <i>d</i>)<sup>b</sup></b>
<b>Eyes score out of 36, 0-2 weeks post intervention (s.d.) (Total sample)<sup>c</sup></b>	23.88 (4.92)	22.97 (5.63)	0.58	0.45	0.18
<b>Eyes score out of 36, 0-2 weeks post intervention (s.d.) (Participants with highest positive letter number sequencing test change 0-2 weeks post-intervention)<sup>d</sup></b>	23.14 (5.28)	21.55 (4.68)	2.33	0.14	0.56
<b>Eyes score out of 36, 0-2 weeks post intervention (s.d.) (Participants with lower or negative letter number sequencing test change 0-2 weeks post-intervention)<sup>e</sup></b>	25.27 (3.97)	24.00 (5.84)	0.19	0.67	0.15

<sup>a</sup>F statistic derived from ANCOVA with Eyes score 0-2 weeks post intervention, as dependent variable, group as independent variable, and Eyes score at baseline, age, gender and baseline IQ as covariates

<sup>b</sup>Cohen's *d* calculation performed using: [https://www.psychometrica.de/effect\\_size.html](https://www.psychometrica.de/effect_size.html)

<sup>c</sup>Sample included 43 CT participants and 35 Control Group participants

<sup>d</sup>Sample included 28 CT participants and 11 Control Group participants



<sup>e</sup>Sample included 15 CT participants and 23 Control Group participants

**Table 4: Neuropsychological results for participants with highest positive letter number sequencing test change 0-2 weeks post-intervention versus participants with lower or negative letter number sequencing test change 0-2 weeks post-intervention.**

	<b>Participants with highest positive letter number sequencing test change 0-2 weeks post-intervention (N = 39) (s.d.)</b>	<b>Participants with lower or negative letter number sequencing test change 0-2 weeks post-intervention (N = 38) (s.d.)</b>	<b>F statistic<sup>a</sup></b>	<b>P value</b>	<b>Effect size (Cohen's <i>d</i>)<sup>b</sup></b>
<b>Letter number sequencing, baseline</b>	6.36 (3.11)	10.08 (3.11)	27.36	<0.001	1.21
<b>Eyes score out of 36, baseline</b>	22.00 (4.66)	22.61 (5.48)	0.47	0.50	0.16

<sup>a</sup>F statistic derived from ANCOVA with letter number sequencing change group as independent variable, baseline letter number sequencing or Eyes score as dependent variable, and age, gender and CT or Control Group as covariates

<sup>b</sup>Cohen's *d* calculation performed using: [https://www.psychometrica.de/effect\\_size.html](https://www.psychometrica.de/effect_size.html)

**Table 5: Faces fMRI participant demographics.**

	<b>CT participants (n = 15)<sup>a</sup></b>	<b>Control Group participants (n = 15)<sup>b</sup></b>	<b>Statistic<sup>c</sup></b>	<b>p value</b>
<b>Mean age in years (s.d.<sup>d</sup>)</b>	45.27 (11.89)	43.27 (11.32)	t = 0.47	0.64
<b>Gender (M:F)</b>	8:7	7:8	$\chi^2 = 0.13$	0.72
<b>Baseline IQ (s.d.)</b>	94.00 (19.51)	94.80 (22.04)	t = 0.11	0.92
<b>Anti-psychotic medication dosage (Chlorpromazine equivalents in m.g. / day) (s.d.)<sup>e</sup></b>	409.30 (471.45)	377.50 (485.48)	t = 0.15	0.88
<b>Mean ART outliers T0 (s.d.)</b>	15.60 (20.59)	9.60 (9.58)	F = 0.46	0.51
<b>Mean ART outliers T1 (s.d.)</b>	9.80 (8.37)	8.00 (6.98)		
<b>SAPS<sup>f</sup> Global Rating of Hallucinations (last month) (s.d.)</b>	1.42 (0.67)	1.07 (0.27)	t = 1.68	0.12
<b>SAPS Global Rating of Severity of Delusions (last month) (s.d.)</b>	1.75 (1.29)	1.67 (1.29)	t = 0.17	0.87
<b>SAPS Global Rating of Severity of Bizarre Behaviour (last month) (s.d.)</b>	1.17 (0.39)	1.36 (0.93)	t = 0.66	0.52
<b>SAPS Global Rating of Positive Formal Thought Disorder (last month) (s.d.)</b>	1.33 (0.89)	2.00 (1.47)	t = 1.42	0.17

<b>SANS<sup>g</sup> Global Rating of Affective Flattening (s.d.)</b>	2.50 (2.07)	1.71 (1.20)	t = 1.16	0.26
<b>SANS Global Rating of Inappropriate Affect (s.d.)</b>	1.00 (0.00)	1.00 (0.00)	n / a <sup>h</sup>	n / a <sup>h</sup>
<b>SANS Global Rating of Alogia (s.d.)</b>	1.83 (1.27)	1.29 (0.83)	t = 1.28	0.22
<b>SANS Global Rating of Avolition (s.d.)</b>	1.92 (1.44)	1.50 (0.94)	t = 0.86	0.40
<b>SANS Global Rating of Anhedonia-Asociality (s.d.)</b>	1.92 (1.78)	1.71 (0.91)	t = 0.37	0.71
<b>SANS Global Rating of Attention (s.d.)</b>	2.17 (1.70)	1.71 (1.14)	t = 0.81	0.43

<sup>a</sup>15 CT participants includes participants with the following diagnosis: 7 schizophrenia, 1 schizoaffective disorder, 3 Bipolar disorder, 1 major depressive disorder, 3 other psychosis

<sup>b</sup>15 Control Group participants includes participants with the following diagnosis: 9 schizophrenia, 1 schizoaffective disorder, 1 bipolar disorder, 1 major depressive disorder, 3 other psychosis

<sup>c</sup>t statistic derived from an independent t-test between groups;  $\chi^2$  value derived from Pearson's chi-squared test with variables group and gender; F values correspond to a time x group interaction performed using a repeated measures ANOVA with within-subject factor time (two levels) and mean ART outliers as measure

<sup>d</sup>s.d. = standard deviation

<sup>e</sup>Chlorpromazine equivalent in m.g./day available for 20 out of 30 participants (10 CT participants and 10 Control Group participants)

<sup>f</sup>Schedule for the assessment of positive symptoms (Andreasen, 1984), available for 12 CT participants and 14 Control Group participants (15 Control participants had Global Rating of

Severity of Delusions data, 14 of these Control participants had data for all of the other variables)

<sup>g</sup>Schedule for the assessment of negative symptoms (Andreasen, 1983), available for 12 CT participants and 14 Control Group participants

<sup>h</sup>t-statistic could not be calculated because the standard deviation of both groups was 0

**Figures.**

**Figure 1: Mean parameter estimates (in arbitrary units) for the faces versus baseline contrast for the Control (CON) and Cognitive Remediation Therapy (CT) Groups, both before (t0) or after (t1) treatment, extracted from three regions of interest (ROIs). See Table 1 for description of ROIs.**

**Figure 2: Mean parameter estimates (in arbitrary units) for the angry versus neutral faces contrast for the Control (CON) and Cognitive Remediation Therapy (CT) Groups, both before (t0) or after (t1) treatment, extracted from three regions of interest (ROIs). See Table 1 for description of ROIs.**

**Figure 3: Mean parameter estimates (in arbitrary units) for the angry faces versus baseline contrast for the Control (CON) and Cognitive Remediation Therapy (CT) Groups, both before (t0) or after (t1) treatment, extracted from three regions of interest (ROIs). See Table 1 for description of ROIs.**

**Figure 4: Mean parameter estimates (in arbitrary units) for the neutral faces versus baseline contrast for the Control (CON) and Cognitive Remediation Therapy (CT) Groups, both before (t0) or after (t1) treatment, extracted from three regions of interest (ROIs). See Table 1 for description of ROIs.**