The remediation effects of working memory training in schizophrenia patients with prominent negative symptoms

Abstract:

Introduction: Negative symptoms, particularly amotivation and anhedonia, are important predictors of poor functional outcome in patients with schizophrenia. There has been interest in the efficacy and mechanism of non-pharmacological interventions to alleviate these symptoms. The present study aimed to examine the therapeutic effect of working memory (WM) training in patients with schizophrenia with prominent negative symptoms.

Methods: Thirty-one schizophrenia patients with prominent negative symptoms were recruited and assigned to either a WM training group or a treatment-as-usual (TAU) control group. The WM training group underwent 20 sessions of training using the dual n-back task over one month. A functional neuroimaging paradigm of the Affective Incentive Delay (AID) task was administered before and after the training intervention to estimate the therapeutic effects of the intervention.

Results: Our results showed that the WM training group demonstrated significant improvement in both trained and untrained WM tasks. Compared with the TAU group, increased brain activations were observed at the right insula and the right frontal sub-gyral after WM training in the training group.

Conclusions: These findings support the efficacy of WM training in ameliorating hedonic dysfunction in schizophrenia patients with prominent negative symptoms.

Keywords: dual n-back training; hedonic processing; anticipatory pleasure; consummatory pleasure; functional magnetic resonance imaging (fMRI)

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1. Introduction

Negative symptoms are disabling features of schizophrenia. In particular, diminished experience of pleasure, i.e., anhedonia, is one of the core features of negative symptoms (Docherty & Sponheim, 2008), and associated with poorer outcomes in patients with schizophrenia (Ritsner, Arbitman, & Lisker, 2011). Recent empirical findings suggest that anhedonia is not a unitary construct but has two distinct subcomponents, namely, anticipatory and consummatory anhedonia, which are subserved by distinct neural mechanisms (Kring & Barch, 2014). Anticipatory pleasure refers to pleasure from future events, whereas consummatory pleasure captures one's momentary emotional reactivity during enjoyable activities (Kring & Caponigro, 2010).

Given these recent findings, there has been a resurgence of interest in examining ways to remediate hedonic dysfunction and other negative symptoms to bring about functional benefits in schizophrenia patients. Currently available treatment, such as antipsychotic medications, has only limited efficacy in alleviating these symptoms (Kirkpatrick, Fenton, Carpenter, & Marder, 2006). Relatively few non-pharmacological interventions have been developed to treat these symptoms (Favrod, Giuliani, Ernst, & Bonsack, 2010; Grant, Huh, Perivoliotis, Stolar, & Beck, 2012; Nguyen et al., 2016) and findings on their efficacy are inconsistent and preliminary.

Recently, there is growing evidence linking cognitive deficits, negative symptoms and neural substrate dysfunction in schizophrenia. Impaired WM is a critical neurocognitive deficit of schizophrenia and neuroimaging studies have identified

altered activities at the prefrontal-subcortical circuit that subserves WM function in these patients (Park and Gooding, 2014). Moreover, evidence from behavioural and neuroimaging studies suggests that WM plays an important role in hedonic processing and goal-directed activities, and WM dysfunction has been found to be significantly correlated with hedonic deficits in patients with schizophrenia (Gold, Waltz, Prentice, Morris, & Heerey, 2008; Kring & Barch, 2014). Abnormal reward processing in schizophrenia patients has also been found to correlate with impairments in affective and value representations, which in turn hamper their ability to translate hedonic experience into motivated behaviours (Gard et al., 2011; Heerey & Gold, 2007). Results from another study (Heerey, Bell-Warren, & Gold, 2008) suggest that WM deficits account for difficulties in weighing potential outcomes effectively during decision making in patients with schizophrenia. In a study that examined the neural correlates of maintenance of emotional stimulus, Ursu et al. (2011) found dysfunction at the prefrontal cortex, the cingulate gyrus and the insula in schizophrenia patients. Further correlational analyses from this study suggest that reduced prefrontal cortex activation was correlated with anhedonia. Altered activations across these regions were also found when patients were asked to perform WM tasks (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Thus, the recruitment of the prefrontal-striatal network in both hedonic processing and WM further supports the association between these two constructs (Barch & Dowd, 2010; McNab & Klingberg, 2008). The identification of the key role and involvement of WM in hedonic processing, therefore, may inform the

design of novel translational intervention to alleviate anhedonia in schizophrenia patients.

Given the important role of WM in general cognition, many training programmes have been developed to improve WM with the aim of generalization. It has been shown that WM training could result in meaningful improvements in domains beyond WM, such as affective control (Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish, 2013), delay discounting (Bickel, Yi, Landes, Hill, & Baxter, 2011) and hedonic processing (Li et al., 2016a; Li et al., 2016b). Interestingly, a shared recruitment of the prefrontal and subcortical system in WM function and affective or reward processing is identified as the neural substrate of transfer (Schweizer et al., 2013; Wesley & Bickel, 2014), suggesting that WM training may have a potential remediation effect on anhedonia and other negative symptoms in schizophrenia patients. In clinical practice, cumulative evidence suggests a generalized beneficial effect of cognitive training on cognitive abilities and community functioning in schizophrenia patients (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Notwithstanding the fact that negative symptoms are influenced to a lesser extent by cognitive interventions, the greatest concern with cognitive remediation therapies is the lack of understanding of the active ingredient that brings about behavioural improvement. On the other hand, findings from studies on WM training coincide with the recently proposed rationale for successful cognitive training programme, which emphasizes the employment of a core brain circuit that supports neural processing for cognitive as well as affective contents

(Vinogradov, Fisher, & de Villers-Sidani, 2012). Furthermore, evidence from studies in non-clinical individuals with social anhedonia suggests that dual n-back training could promote their behavioural sensitivity towards positive affective contents (Li et al., 2016b) and could strengthen brain activations during anticipation of future events (Li et al., 2016a). These findings highlight the potential of dual n-back task training as a candidate for successful intervention. However, the studies by Li et al. (2016a; 2016b) were limited to non-clinical samples and it is unclear whether dual n-back training could alleviate anhedonia in schizophrenia patients with prominent negative symptoms.

The present study aimed to investigate the potential neural transfer effects of WM training in alleviating anhedonia in schizophrenia patients with prominent negative symptoms. A recent neuroimaging meta-analysis focusing on the neuroplastic effect of WM training suggests that brain regions showing neuroplasticity in schizophrenia overlap with those in healthy volunteers (Li et al., 2015). Given previous findings on dual n-back training in people with social anhedonia, we hypothesized that behavioural performances in both trained and untrained cognitive tasks would be enhanced in patients with schizophrenia with WM training. We also hypothesized that the neural processing of hedonic experience in schizophrenia would be enhanced after WM training. To test our hypotheses, the Affective Incentive Delay (AID) task, which specifically captures temporal neural activations during the active processing of affective incentives (Chan et al., 2016), was administered to all participants at baseline

and after training.

2. Methods

2.1. Participants

Patients diagnosed with schizophrenia according to *DSM-IV* (American Psychiatric Association, 1994) were recruited from the Shanghai Mental Health Centre. Eligible patients were invited to take part in the study and then screened based on the following inclusion criteria: 1) ≤ 50 years of age; 2) ≥ seven years of education; 3) estimated IQ ≥ 70; 4) no history of drug abuse; 5) no history of neurological disorders or brain injury; and 6) no history of electroconvulsive therapy in the past three months. Moreover, to be considered as having prominent negative symptoms, participants must meet the following two additional criteria based on scores on the Positive and Negative Syndrome Scale (PANSS) (Kay, Flszbein, & Opfer, 1987): 1) PANSS negative subscale score ≥ 6 points over PANSS positive subscale score; and 2) fewer than three items with score ≥ 3 (mild) on the PANSS positive subscale (Olie, Spina, Murray, & Yang, 2006). Thirty-one schizophrenia patients were included and 16 patients were assigned to a WM training group, while the remaining 15 patients were assigned to the treatment-as-usual (TAU) group which received only pharmacotherapy. One patient in the WM training group received modified electroconvulsive therapy (MECT) after baseline assessment and was therefore excluded. Four patients in the TAU control group did not attend the assessment session for a second time due to scheduling problems. In the end, the final sample comprised 26 individuals for whom

complete data were available. Patients in the WM training group received 20 sessions of 20-30 min computerized WM training for four weeks in addition to pharmacotherapy. A set of comprehensive assessment was administered to all patients in both groups before and after training.

The study was approved by the Ethics Committee of the Shanghai Mental Health Centre and the Institute of Psychology, Chinese Academy of Sciences. All participants gave written informed consent.

2.2. Procedures and measures

2.2.1. Training procedure: the dual n-back task

WM training was conducted using the dual n-back task. Details of the training protocol have been described by Li et al. (2016b). In brief, simultaneous visual–auditory stimuli were displayed and participants were asked to indicate whether the current visual and/or auditory stimuli were the same as the one presented n positions back, such that modality-independent responses should be made from trial to trial. Each block had *n* + 20 trials, including six visual and six auditory target trials (four visual or auditory target trials separately and two trials of both visual and auditory target), and *n* was the same for both modalities. Participants completed 20 blocks in each session, with each session lasting 20-30 minutes. Each session started with *1*-back, and the value of *n* in the following block increased or decreased adaptively depending on the participant's performance. An auditory feedback was provided immediately if a

target was correctly detected.

2.2.2. Clinical assessments

Ratings on the PANSS and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982) were made by experienced psychiatrists to assess the severity of schizophrenia symptoms. Side effects of antipsychotic medications were estimated using the Abnormal Involuntary Movements Scale (AIMS) (Smith, Kucharski, Oswald, & Waterman, 1979) and the Barnes Akathisia Rating Scale (BARS) (Barnes, 1989).

2.2.3. Cognitive measures

To assess changes in cognitive functions, the Letter Number Span (LNS) task (Chan et al., 2008; Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997), the Logical Memory subtest of the Wechsler Memory Scale-3rd (WMS-III) (Wechsler, 1997), and the Verbal Fluency task were administered to all participants. Immediate and 30-minute delay retention scores on the Logical Memory subtest were recorded. The Verbal Fluency task measures executive function and participants were asked to name as many different animals as possible within 60 seconds. Estimated IQ was assessed with the four-subtest short form of the Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Gong, 1992).

2.2.4. Self-report measures

The Chapman Social Anhedonia Scale (CSAS) (Chan et al., 2012; Eckblad, Chapman, Chapman, & Mishlove, 1982) and the Temporal Experience of Pleasure Scale

(TEPS) (Chan et al., 2012; Gard, Gard, Kring, & John, 2006) were administered to assess hedonic capacities. Higher scores on the CSAS indicate more severe deficits in hedonic experiences derived from social interactions, while higher scores on the TEPS indicate greater degree of hedonic experience. The Emotional Expressivity Scale (EES) (Chan et al., 2010; Kring, Smith, & Neale, 1994) was used to estimate the degree of outward display of emotions with two subscales: "emotional expression" and "emotional suppression". The Emotion Regulation Questionnaire (ERQ) (Gross & John, 2003; Wang, Liu, & Li, 2007) was used to evaluate an individual's preferential use of adaptive (reappraisal) and maladaptive (suppression) strategies to regulate their emotions and expressive behaviours. The Beck Depression Inventory-I (BDI-I) (Beck, Ward, & Mendelson, 1961) was used to measure the severity of depressive symptoms.

2.2.5. Hedonic processing neuroimaging paradigm

The AID task was conducted before and after the completion of training for both the WM training and TAU groups. We adapted the Monetary Incentive Delay (MID) paradigm (Knutson, Westdorp, Kaiser, & Hommer, 2000) to assess anticipatory approaches and consummatory pleasure to affective incentives with positive or negative valence. Details of this task can be found in our previous publication (Chan et al., 2016). In brief, a cue (triangle, square or circle) indicating the positive, negative, or neutral condition was first presented for 250ms. This was followed by a delay period capturing anticipatory related brain activity, lasting for 2000ms to 2500ms. Then a blue target was displayed and participants were instructed to press a button with their right

index finger as quickly as possible. In the first trial, the duration of the target was decided with a simple reaction time (RT) task in which participants were required to press a button as soon as they saw the blue target (30 trials), while the duration of the target in the subsequent trials was adjusted based on the individual's mean RT and accumulative accuracy in previous trials to achieve a total accuracy rate of approximately 66.7%. Affective images with positive, negative or neutral valence were then shown for 3000ms as feedbacks, depending on the cue type and individual's RT. A random inter-trial interval ranging from 2500ms to 5500ms was adopted. Each trial lasted for 12s. The emotional stimuli utilized were selected from the International Affective Picture System (IAPS) (see Xie et al. (2014) for their valence and arousal information). The task consisted of two runs, with 10 positive, negative and neutral conditions randomly presented in each run.

2.2.6. Images acquisition and data preprocessing

The imaging data were acquired using a 3-Tesla Siemens Verio MRI scanner at the Shanghai Mental Health Centre. TheT1-weighted structural scans were collected with the following parameters: repetition time (TR): 2,530 ms, echo time (TE): 1.66 ms, field of view (FOV): 256 mm, flip angle: 7°, image matrix: 256 × 256, and slice thickness: 1 mm. Functional neuroimaging data were collected with a whole-brain echo planar imaging (EPI) sequence: TR: 2,000 ms, TE: 30 ms; FOV: 210 mm, slices: 31, flip angle: 90°, image matrix: 64 × 64, and voxel size: 3.3 × 3.3 × 4 mm^3.

Imaging data were preprocessed using the Statistical Parametric Mapping

software package (SPM8; Wellcome Department of Imaging Neuroscience, London, UK) by the following steps: head motion correction, slice timing, co-registration to structural image, and smoothing using 8-mm full-width at half maximum Gaussian Kernel. Movement outliers (scan to scan movement greater than 0.6 mm) or spike artifacts (absolute movement greater than 3 mm) were identified with the Artifact Detection Tool (ART). Less than 10% variation was observed in each run, and so data of all the participants were included in the final analysis.

2.3. Statistical analysis

Behavioural data were analyzed using SPSS (17.0 for Windows, SPSS Inc., Chicago, IL, USA). Baseline characteristics of these two groups were compared using independent sample *t*-tests (two tailed). Training effects on cognitive tests and self-report questionnaires were analyzed with mixed analysis of variances (ANOVAs).

For individual level analyses of the functional magnetic resonance imaging (fMRI) data, a haemodynamic response function with nine conditions of interest (positive cue, negative cue, neutral cue, positive cue hit, positive cue miss, negative cue hit, negative cue miss, neutral cue hit, neutral cue miss) and seven head movement parameters as covariates of no interest (six realignment parameters and one ART regressor) were modelled separately in each run for each participant Then, the contrasts “positive cue > neutral cue” and “negative cue > neutral cue” were established to examine brain activations related to anticipation for positive and negative affective incentives

respectively. Finally, the contrasts “positive cue hit > neutral cue hit” and “negative cue miss > neutral cue miss” were established to identify brain activations during consummation of positive and negative affective outcomes respectively.

For group level analyses, differences in brain activations across these contrasts at baseline were compared between these two groups using SPM independent *t*-tests. Paired t-tests were used to compare activation changes from baseline to post-training session within the training group. These analyses were thresholded at $p < 0.001$ (uncorrected) and a spatial extent threshold of 10 voxels was adopted. This threshold is consistent with previous literature (Chen et al., 2016; Tseng et al., 2015), but may limit our control of false positives (Eklund, Nichols, & Knutsson, 2016). Then the percentage signal changes from clusters demonstrating significant pre-post changes were extracted for each condition and participant separately and tested for training specific effects of the WM training in the Group X Session interaction. Moreover, signals from clusters showing the above interactions were correlated with reduction in score on the SANS and the PANSS negative subscale to examine the relationships between brain activation changes and negative symptom reduction from WM training. Since we predicted that our outcomes would be negatively related *a-priori*, one-tailed Pearson correlations were performed with all variables standardized.

3. Results

3.1. Baseline behavioural and fMRI findings

Table 1 summarizes the demographic and clinical features, as well as performances on cognitive and self-report measures of the study sample. The WM training and TAU groups did not differ significantly in baseline characteristics or baseline cognitive and self-report measures. However, the WM training group exhibited significantly more severe attention deficit on the SANS Inattention subscale than the TAU group (t (15.62) = 3.390, p = .004, d = 1.209).

During fMRI scanning, these two groups showed no difference in RTs or accuracy on the AID task (all ps > 0.05) (see Table S1 in supplementary materials). Significant brain activations during the anticipatory and consummatory phases within the WM training and TAU control groups at the pre-training session can be found in Supplementary Table S2. Significant between-group differences in brain activation were observed during the consummatory phase only (Supplementary Table S3). Compared with the TAU group, the WM training group showed hyper-activation when viewing positive affective images at the left medial frontal gyrus, the right fusiform gyrus, the right superior parietal gyrus and the left hippocampus. These baseline group differences, for obvious reasons, could not be due to WM training, but may reflect some unspecified differences between these two groups.

3.2. Training gains on the dual n-back task

A gradual and significant improvement was observed during the 20-session training (Figure 1). The average daily maximum n was 2.47 (SD = 0.52) in the first

training session, which increased significantly to 3.93 (*SD* = 1.10) in the last session (*F* (19, 266) =12.744, $p < 0.001$, partial $\eta^2 = 0.477$).

3.3. WM training effects on behavioural measures

We observed no specific effect of WM training on PANSS-measured symptomatology in the WM training group compared with the TAU group. However, there was a significant interaction between Group and Session (*F* (1, 24) = 6.613, $p = 0.017$, partial $\eta^2 = 0.216$) for scores on the Inattention subscale of the SANS (Table 2). Post-hoc analyses revealed a significant reduction in attention deficits in the WM training group ($p = 0.012$), but not the TAU controls ($p = 0.301$). Regarding gains on cognitive and self-reported measures, significant Group X Session interactions were found for the LNS task (*F* (1, 24) = 7.509, $p = 0.011$, partial $\eta^2 = 0.238$) and total score on the EES (*F* (1, 24) = 4.619, $p = 0.042$, partial $\eta^2 = 0.161$) (see Figure 2). Post-hoc analyses indicated a significant improvement on the LNS task after training for the WM training group ($p = 0.032$), but not the TAU group ($p = 0.110$). Moreover, compared with the TAU group, patients in the WM training group were more emotionally expressive at post-training, as measured by the EES ($p = 0.017$).

3.4. Training effects on hedonic processing

No significant training effects were found at the behavioural level for RTs or accuracy on the AID task.

Figure 3 illustrates the brain regions that showed activation changes in the AID task related to WM training. Increase in brain activations was found at the right insula for the "positive cue > neutral cue" contrast during anticipation, and at the right frontal sub-gyral, the left superior temporal gyrus and the left middle temporal gyrus for the "positive cue hit > neutral cue hit" contrast (see Supplementary Table S4). No activation changes were found for other contrasts. Signals of these clusters were then extracted and analyzed using a series of Session (pre-training vs. post-training) x Group (WM group vs. TAU controls) mixed ANOVAs. These analyses revealed significant Session x Group interactions at the right insula, adjacent to the temporo-parietal junction (F (1, 24) = 5.202, p = 0.032, partial η^2 = 0.178) and at the right frontal sub-gyral (F (1, 24) = 6.061, p = 0.021, partial η^2 = 0.202). Post-hoc analyses revealed significant increase in brain activations for the WM training group (p = 0.003, p = 0.002), but not the TAU group (p = 0.881, p = 0.781). To test whether training effects were confounded by baseline activation differences, we compared brain activations across these regions at pre- and post-training sessions with small volume correction. No significant changes in brain activation were found for these clusters. Thus, baseline group differences of brain activation did not significantly confound our results.

To examine the relationships between brain activation changes and negative symptom reduction resulting from WM training, signals from clusters showing the above interactions were correlated with reduction in score on the SANS and the PANSS negative subscale. A significant inverse correlation was found between decreased

severity on the affective flattening/blunting subscale of the SANS and increase in insula activation (r = -0.509, p = 0.026). Moreover, score changes on the PANSS negative subscale correlated significantly and negatively with brain activation increase at the frontal sub-gyral (r = -0.496, p = 0.030, see Figure 4).

4. Discussion

This study examined the potential therapeutic efficacy of WM training on anhedonia and general cognition in schizophrenia patients with prominent negative symptoms. We observed substantial training-induced improvement on WM capacity and attention in the WM training group. Moreover, analyses of neuroplastic effects on hedonic processing revealed elevated brain activations at the right insula and the frontal sub-gyral in the WM training group. Results of correlational analyses further confirmed the association between elevated brain activities in these two regions and reduction in negative symptoms. Taken together, our results support the efficacy of WM training in alleviating hedonic deficits in schizophrenia patients with prominent negative symptoms.

We found that schizophrenia patients could benefit from WM training and significant improvement in performance on the training task was observed. This is consistent with findings from other studies (Hubacher et al., 2013; Wexler, Anderson, Fulbright, & Gore, 2000). Schizophrenia patients exhibit WM dysfunction and functional hypofrontality when undertaking tasks that engage WM (Deserno, Sterzer,

Wustenberg, Heinz, & Schlagenhauf, 2012). The adaptive training regime used in this study required participants to continuously adjust to the increasing demands of WM. Thus they could encode, monitor and update WM contents more efficiently at the end of the training. The efficacy of dual n-back training have been investigated previously in the healthy population and it was suggested that the neural efficiency of the frontoparietal demand network underlying WM function is enhanced after training (Schweizer et al., 2013). Additionally, we also observed generalized improvement in an untrained WM task and a clinical assessment instrument that measures inattention symptom in schizophrenia patients in the WM training group. This finding is in line with findings from the cognitive remediation literature (Wykes et al., 2011). Importantly, our results suggest that improvement in WM function may be one of the active ingredients that lead to general improvement from cognitive remediation. However, significant changes were not observed for logical memory and verbal fluency in the WM training group. It is also noteworthy that the extent of performance improvement in the training task in schizophrenia patients is less than that found in individuals with social anhedonia (Li et al., 2016a; Li et al., 2016b). It is possible that other impairments in neurocognitive functions in schizophrenia patients may impede their capacity to benefit from WM training.

Regarding the neuroimaging results, significant activation changes were observed at the right insula during the anticipatory phase in the WM training group. Both the frontal-parietal circuitry and the insula are associated with core WM functions

(Rottschy et al., 2012). Alterations in cortical thickness of the frontal-parietal network and the insula have been reported after two months of adaptive WM training in healthy individuals (Metzler-Baddeley, Caeyenberghs, Foley, & Jones, 2016). A study using real-time fMRI suggests that WM training induce enhanced functional connectivity between the insula and key nodes of the central executive network and the default mode network (Zhang, Zhang, Yao, & Zhao, 2015). Our findings that after WM training schizophrenia patients activated the insula more than controls are consistent with results from a recent meta-analysis examining brain correlates of cognitive remediation in schizophrenia, which also reported increased activation at the insula after cognitive training (Ramsay & MacDonald, 2015).

Another previous study has found that the insula is involved in the anticipation and evaluation of emotional contents and social cognition (Wylie & Tregellas, 2010). Decreased insula activation during reward anticipation has also been found in patients with schizophrenia and their unaffected siblings (de Leeuw, Kahn, & Vink, 2014). In performing tasks capturing empathy and theory of mind, the insula was found to be significantly less activated in schizophrenia patients (Benedetti et al., 2009). Furthermore, in a structural neuroimaging study investigating brain structure abnormality, Sigmundsson et al. (2001) reported volume reduction at the insula in schizophrenia patients with prominent negative symptoms. Thus, these functional and structural aberrations of the insula may represent a key feature in schizophrenia.

On the other hand, recent literature indicates that WM correlates with empathic

capacity and WM deficits contribute significantly to poor social functioning in patients with schizophrenia (Smith et al., 2013). This suggests an interaction between WM and social information processing. It has been reported that schizophrenia patients with higher WM capacity tend to maintain more positive than negative information (Xie et al., 2016). As such, the increased insula activation after WM training we observed may be a reflection of enhanced representation of value information for positive emotions that helps to consolidate the connection between cues and outcomes. Furthermore, patients in the training group rated themselves to be more expressive emotionally than controls after WM training, and results of correlation analyses revealed an association between increased insula activation and reduction in affective flattening. These results provide convergent evidence for improved processing of socioemotional information after WM training. A recent study using real-time fMRI found that schizophrenia patients could up-regulate activation at the anterior insula through neurofeedback training, and the increased insula activation was correlated with better ability in the identification of facial emotion expressions (Ruiz et al., 2013). Therefore, our findings, together with those reported by previous studies, support that there remains residual neuroplasticity in patients with schizophrenia. Moreover, our results are also consistent with previous research which shows that dual n-back training could enhance anticipatory sensitivity to positive affects in psychometrically-defined schizotypal individuals to the level of controls (Li et al., 2016a; Li et al., 2016b). The involvement of active maintenance of WM for hedonic content and goal-directed

behaviours (Kring & Caponigro, 2010), and the overlapping recruitment of the prefrontal-striatal system in WM and hedonic processing may underlie the behavioural and neuroplastic effects observed in our study. Further research is needed to incorporate WM tasks during brain scanning to advance our understanding of the training effects related to these neural substrates.

We also observed significantly increased activation at the frontal sub-gyral when participants in the WM training group viewed positive affective images. Previous studies have also demonstrated that increased activation in frontal white matter were correlated with higher attractiveness ratings of faces, indicating the involvement of frontal white matter in social reward evaluation (Smith et al., 2014). Thus, the increased activation at the frontal sub-gyral after WM training may be a reflection of enhanced efficiency in the processing of positive emotions in schizophrenia patients. However, in another study, Cheng et al. (2015) interpreted changes in white matter functional activities as physiological noise. The neurophysiological nature of white matter fMRI signals is not clearly known, and further study of white matter activations may provide a new avenue for the understanding of brain plasticity in clinical samples characterized by white matter changes.

It should be noted that our results remain preliminary as training-related changes were not found for self-reported hedonic experience (viz., CSAS and the TEPS) or emotion regulation. Apart from hedonic processing deficits, schizophrenia patients show a preferential use of suppression when regulating affect and tend to use

reappraisal less frequently (van der Meer, Wout, & Aleman, 2009). A neuroimaging study by van der Meer et al. (2014) further revealed an abnormal activation pattern at the insula, the ventral lateral prefrontal cortex and the middle temporal gyrus in schizophrenia patients when they were instructed to reappraise negative emotional stimuli. It is noteworthy that WM training studies in individuals with schizotypy also did not find any positive transfer to self-reported measures of emotions (Li et al., 2016a; Li et al., 2016b), which suggests that self-reported pleasure experiences might not be sensitive for training-related changes in hedonic processing. It is also possible that severe negative symptoms in our sample limited the participants' ability to adopt more adaptive regulation strategies, as schizophrenia patients with more severe negative symptoms demonstrate greater difficulty in volitional control to activate the anterior insula (Ruiz et al., 2013).

There are several limitations of the present study. First, our sample size was small and we were underpowered to detect significant improvements for all dimensions of negative symptoms and self-reported emotions. Secondly, participants in the TAU group received the usual pharmacotherapy only. As a result, the training effect might have been confounded by motivation, computer exposure or meeting frequency with the experimenter. However, meta-analysis of WM training in healthy adults did not reveal any significant difference in improvement across different control groups (active vs. passive) (Soveri, Antfolk, Karlsson, Salo, & Laine, 2017). Thirdly, the lack of follow-up assessments makes it difficult to determine whether the training effects

could be sustained over time. Fourthly, the PANSS negative subscale and the SANS were used to assess negative symptoms in this study. Future study should adopt newly developed outcome measures such as the Clinical Assessment Interview for Negative Symptoms (Kring, Gur, Blanchard, Horan, & Reise, 2013). Finally, only patients with prominent negative symptoms were recruited, which might limit the generalizability of our results.

In conclusion, our behavioural and brain imaging results support our hypotheses that neurocognitive impairments in schizophrenia, particularly those related to anhedonia may benefit from WM training. To the best of our knowledge, this is the first study that shows that hedonic processing dysfunction in schizophrenia patient could be alleviated with WM training. The integration of WM training with other interventions, such as anticipatory pleasure skills training, may offer novel approaches for the treatment of anhedonia and could benefit patients with hedonic deficits.

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Declaration of interest statement

None

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Figure captions

Fig 1. The average daily max *n*-level reached on the dual *n*-back task across the 20 training sessions in the WM training group. Error bars represent standard error.

Fig 2. Performance on the Letter Number Span (LNS) task (3.A) and total score of the the Emotional Expressivity Scale (EES) (3.B) in the training and control groups at pre- and post-training sessions. Error bars represent standard error.

Fig 3. Brain regions showing significant activation changes from pre- to post-training sessions in the WM training group.

Fig 4. Correlation between brain activation changes (% signal change) and negative symptom reduction from pre- to post-training sessions in schizophrenia patients of the WM training group. All values are Z-standardized.

Table 1 demographic and clinical characteristics, measures for cognitive function and self-reported checklists (*mean*±*SD*) of schizophrenia patients

	WM training group (n = 15)		TAU control group (n = 11)		Baseline Group Difference Analysis			Training Effect Analysis (Group x Session interaction)		
	pre-training	post-training	pre-training	post-training	*t/χ2*	*p*	*Cohen'd*	*F*	*p*	*Partial* η^2
Gender(male/female)	8/7		8/3		2.275	0.131				
Age	26.33±7.65		29.55±8.41		-0.649	0.523	0.268			
Education (years)	14.47±3.29		12.91±3.02		1.369	0.184	0.566			
Illness Duration (years)	4.67±4.46		4.34±4.11		0.116	0.908	0.048			
IQ estimation	112.57±18.73		105±12.94		0.904	0.375	0.374			
Antipsychotic Medication (n, first generation/second generation/multiple)[a]	1/14/0		0/10/0							
Medication dosage (chlorpromazine equivalence, mg)	292.53±279.71		196.96±151.44		1.025	0.316	0.423			
AIMS	0.80±1.37	0.60±1.12	0.45±0.93	0.45±0.82	0.719	0.479	0.285	0.112	0.741	0.005
BARS	0.87±1.19	0.60±1.18	0.27±0.65	1.00±1.34	1.635	0.116	0.619	2.944	0.099	0.109
Letter Number Span	15.27±3.04	16.87±3.34	15.73±4.98	14.36±3.64	-0.293	0.772	0.121	7.509	0.011	0.238
Logical Memory (immediate)	11.07±4.1	13.93±3.43	10.73±5.87	13.73±4.5	0.174	0.863	0.072	0.009	0.926	0.000
Logical Memory (delay)	7.93±4.27	11.27±4.08	8.64±5.39	12.64±4.9	-0.371	0.714	0.153	0.336	0.567	0.014
Verbal fluency [b]	17.27±5.11	19.47±4.98	17.4±3.72	20.1±4.12	-0.071	0.944	0.030	0.079	0.781	0.003
CSAS	14.87±4.66	10.4±5.99	18.55±5.34	13.09±6.11	-1.872	0.074	0.773	0.208	0.652	0.009
BDI-I	8.47±6.5	3.87±3.96	11±7.09	7.45±7.03	-.945	0.354	0.391	0.209	0.652	0.009
TEPS total score	73.27±12.91	77.2±12.65	67±28.32	76.64±13.48	0.760	0.455	0.314	0.976	0.333	0.039
Anticipatory pleasure	33.6±6.1	34.73±5.04	30.64±7.59	33.91±7.13	1.104	0.281	0.456	1.341	0.258	0.053
Consummatory pleasure	39.67±7.62	42.47±8.1	38.55±17.17	42.73±12.39	0.202	0.843	0.083	0.120	0.732	0.005

EES total score		65.07±8.66	68±6.3	64.18±6.98	61.18±7.15	0.278	0.783	0.115	4.619	0.042	0.161
	EES expression	18.87±4.42	20.2±3.84	19.91±5.8	19.18±4.17	-0.521	0.607	0.215	1.186	0.287	0.047
	EES suppression	30.8±7.38	29.2±4.25	32.73±4.73	35±5.6	-0.757	0.456	0.313	2.760	0.110	0.103
ERQ total score		41.07±5.91	41.2±6.16	44.91±10.45	46.18±6.15	-1.192	0.245	0.492	0.119	0.733	0.005
	ERQ reappraisal	26.8±3.49	27.27±5.01	28.91±6.16	30.09±3.36	-1.111	0.278	0.459	0.107	0.746	0.004
	ERQ suppression	14.27±3.17	13.93±2.79	16±5.14	16.09±4.89	-1.063	0.298	0.439	0.056	0.815	0.002

[a] one participant in the TAU group were not taking antipsychotic medication treatment at the time of the baseline assessment.

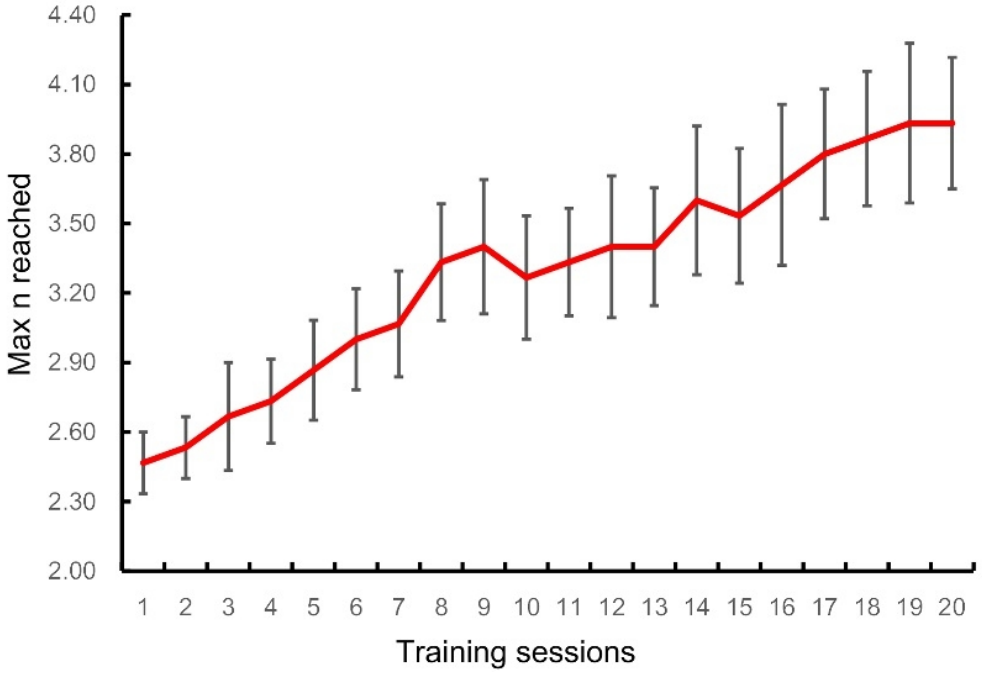
[b] Data of one participant in the TAU control group was missing on the verbal fluency task.

Abbreviations: TAU: treatment-as-usual; AIMS: Abnormal Involuntary Movement Scale; BARS: Barnes Akathisia Rating Scale; CSAS: the Chapman Social Anhedonia Scale; BDI-I: The Beck Depression Inventory-I; TEPS: the Temporal Experiences of pleasure scale; EES: the Emotional Expressivity Scale; ERQ: the Emotion Regulation Questionnaire.

Table 2 descriptive statistics (*mean*±*SD*) on clinical measures at pre- and post-training sessions in all participants

	WM training group		TAU control group		Baseline Group Difference Analysis			Training Effect Analysis (Group x Session interaction)		
	pre-training	post-training	pre-training	post-training	*t*	*p*	*Cohen'd*	*F*	*p*	*Partial* η^2
PANSS total score	56.93±8.61	50.87±9.73	58.73±3.38	56.82±8.42	0.653	0.52	0.27	1.116	0.301	0.044
Positive	8.2±1.47	8.4±2.17	7.82±2.68	8.45±2.07	0.466	0.645	0.193	0.604	0.176	0.679
Negative	21.93±4.86	17.27±4.62	23.45±2.58	21.36±3.61	0.941	0.356	0.389	2.338	0.139	0.089
General psychopathology	26.8±5.36	25.2±5.45	27.45±2.25	27±4.31	0.379	0.708	0.157	0.228	0.638	0.009
SANS total score	27.47±6.65	20.13±6.94	27.64±3.8	23.64±3.7	0.076	0.94	0.031	1.507	0.232	0.059
Affective Flattening/Blunting	9.33±2.53	7.53±2.8	9.73±0.65	9.36±1.57	0.579	0.571	0.208	2.082	0.162	0.08
Alogia	6.8±2.46	4.93±2.6	7.82±1.47	6.45±1.57	1.316	0.201	0.504	0.253	0.619	0.01
Avolition/Apathy	8.67±2.44	6.6±2.26	9.55±1.97	7.82±1.47	0.982	0.336	0.406	0.155	0.697	0.006
Asociality/Anhedonia	10.07±1.62	7.67±3.11	10.09±1.64	8.73±1.49	0.037	0.97	0.015	0.869	0.360	0.035
Inattention	1.93±1.94	0.93±1.10	0.18±0.4	0.64±1.57	3.39	0.004	1.209	6.613	0.017	0.216

Abbreviations: TAU: treatment-as-usual; PANSS: The positive and negative syndrome scale; SANS: the Scale for the Assessment of Negative Symptoms.



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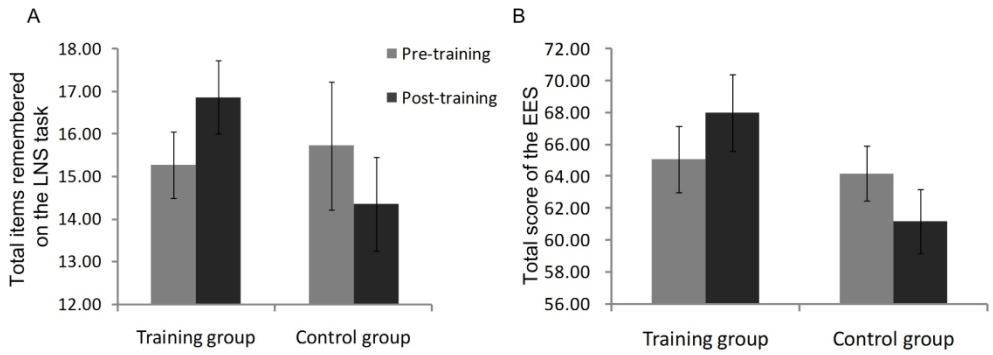

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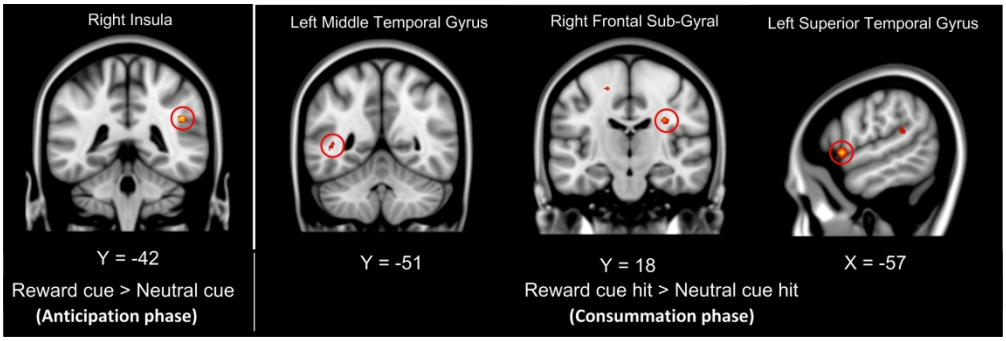

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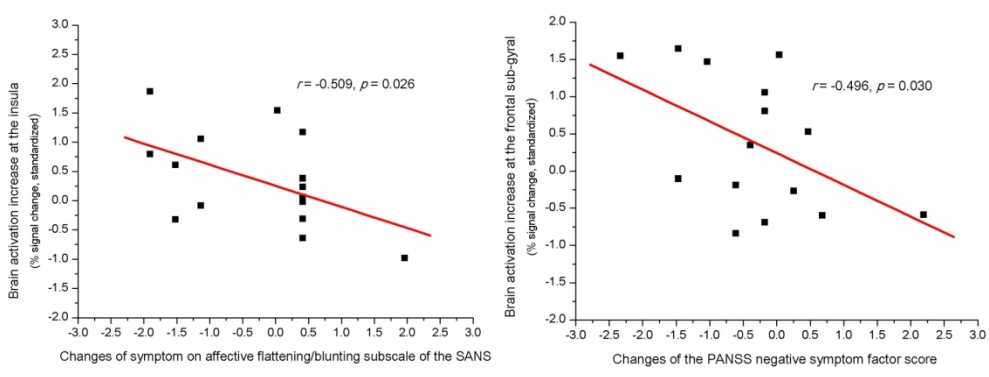

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Table S1 behavioral performance (Mean ± SD) on the AID task in the MRI scanner

	WM training group (n= 15)		TAU control group (n = 11)	
	pre-training	post-training	pre-training	post-training
RTs (ms)				
Control	239.67±37.98	228.72±25.33	228.94±33.12	230.12±24.36
Negative	241.02±49.56	231.17±28.1	232.58±31.8	228.33±35.67
Positive	231.67±39.55	228.61±21.94	232.73±24.01	222.66±30.26
Accuracy (%)				
Control	61±10.04	60.67±7.29	68.64±8.09	64.55±8.5
Negative	61.67±16.11	57.67±6.51	63.64±10.98	63.18±8.45
Positive	65.33±10.43	62.33±7.53	63.64±5.95	63.18±4.62

Abbreviations: The AID task: the affective incentive delay task; WM: working memory; TAU: treatment-as-usual

Table S2 Brain activation in the anticipation and consummation phases in the WM training group (TG) and the TAU control group (CG) at pre-training session

Group	Contrast	Numbers of Sig. Clusters	Cluster Size	X	Y	Z	peak *t*	brain Regions	Brodmann's Area
TG	**Anticipation phase**								
	Positive cue > Neutral cue	2	11	-33	-81	-12	5.530	Inferior Occipital Gyrus	18/19
			27	30	-87	-3	5.471	Middle Occipital Gyrus	18
				42	-81	-6	4.580		
	Negative cue > Neutral cue	0							
	Consummation phase								
	Positive cue hit > Neutral cue hit	6	1765	51	-69	0	12.952	Inferior/Middle Temporal Gyrus	37/19
				45	-54	6	10.927		
				-51	-72	12	9.319		
			35	48	6	39	6.191	Inferior Frontal Gyrus	9
			10	21	0	-18	5.637	Parahippocampus	
			46	-6	57	27	5.630	Superior Frontal Gyrus	9/10
				-12	54	39	4.965		
				3	57	27	4.228		
			16	-36	24	-21	4.377	Superior Temporal Gyrus	38
				-48	18	-21	4.272		
			17	39	30	-15	4.359	Inferior Frontal Gyrus	47
				42	21	-18	4.202		
	Negative cue miss > Neutral cue miss	6	29	51	9	39	5.123	Inferior Frontal Gyrus	9
				45	3	33	4.817		
			53	-54	-60	6	4.723	Middle Temporal Gyrus	21

					-45	-63	9	4.581	
				32	48	-54	6	4.700	Middle Temporal Gyrus	39/22
				10	-51	24	12	4.538	Inferior Frontal Gyrus	
				10	42	-48	-15	4.479	Fusiform Gyrus	
				21	51	-66	-3	4.155	Middle Temporal Gyrus	37
CG	**Anticipation phase**									
	Positive cue > Neutral cue	0								
	Negative cue > Neutral cue	1	15		51	-18	0	5.624	Superior Temporal Gyrus	
	Consummation phase									
	Positive cue hit > Neutral cue hit	4	274		48	-66	3	7.973	Middle Temporal Gyrus	19/37
					42	-78	-6	7.151		
					33	-90	-9	5.850		
				26	-51	-57	15	7.602	Middle Temporal Gyrus	19
				15	42	-42	-18	5.939	Fusiform Gyrus	37
				35	-9	-99	-3	5.685	Lingual Gyrus	17
					-24	-93	-12	5.057		
					-15	-87	-12	4.564		
	Negative cue miss > Neutral cue miss	6	109		42	-72	-3	7.124	Middle Temporal Gyrus	19/37
					48	-57	-3	5.662		
					48	-60	9	4.378		
				14	42	-42	-18	6.764	Fusiform Gyrus	37
				29	-21	-33	-6	6.395	Parahippocampus	
					-18	-24	-9	5.121		
					-30	-27	-6	4.714		
				18	-39	-48	-21	5.955	Fusiform Gyrus	37
				21	-54	-51	12	5.655	Middle Temporal Gyrus	39/22

22	-9	-48	21	5.566	Posterior Cingulate
	3	-54	24	4.631	

Table S3 Comparisons of brain activation differences in the anticipation and consummation phases between the WM training group (TG) and the TAU control group (CG) at pre-training session

Conditions	Contrast	Numbers of Sig. Clusters	Cluster Size	X	Y	Z	Peak *t*	Brain Regions
Anticipation phase								
Positive cue > Neutral cue								
	TG>CG	0						
	CG>TG	0						
Negative cue > Neutral cue								
	TG>CG	0						
	CG>TG	0						
Consummation phase								
Positive cue hit > Neutral cue hit								
	TG>CG	4	48	-6	-30	69	6.153	Medial Frontal Gyrus
			13	-21	-33	-3	4.794	Hippocampus
			28	30	-63	-18	4.507	Fusiform Gyrus
				42	-57	-15	3.836	
			16	24	-78	48	4.159	Superior Parietal Lobule
				33	-75	42	3.599	
	CG>TG	0						
Negative cue miss > Neutral cue miss								
	TG>CG	0						
	CG>TG	0						

Table S4 Brain regions showing significant activation changes from pre- to post-training session in the WM training group

Contrasts	Numbers of Sig. Clusters	Cluster Size	X	Y	Z	Peak *t*	Laterality	Brain Regions
Anticipation phase								
Positive cue > Neutral cue	1	12	48	-42	27	4.475	Right	Insula
Negative cue > Neutral cue	0							
Consummation phase								
Positive cue hit > Neutral cue hit	3	12	-57	12	0	7.545	Left	Superior Temporal Gyrus
		11	30	-18	27	6.182	Right	Frontal Sub-Gyral
		10	-42	-51	6	4.42	Left	Middle Temporal Gyrus
			-42	-45	15	4.238	Left	
Negative cue miss > Neutral cue miss	0							