Improving motivation through real-time fMRI based self-regulation of the nucleus accumbens

Abstract

Objective: Impaired nucleus accumbens (NAcc) activation is associated with amotivation and anhedonia which are resistant to treatment with antipsychotics and antidepressants in schizophrenia. In this study, healthy participants were trained to self-regulate the activation of their NAcc, a brain region that plays an important role in motivation, using real-time fMRI neurofeedback.

Method: The experimental group (N=19) received feedback from the NAcc, while the control group (N=5) received 'sham' feedback from the posterior parahippcampal gyrus, a control brain region not normally related to motivation. All participants were trained to use mental strategies to regulate their NAcc activations in a 3T MRI scanner.

Results: For the learning effect of NAcc regulation, we found that the majority of participants (74%) in the experimental group successfully learned to self-regulate the NAcc. They also showed improved behavioural performance in motivation and decreased functional connectivity between the NAcc and the ventral medial prefrontal cortex and an increase in small world properties in the reward circuit after training, indicating improved information integration in reward processing. However, improvement in motivation and modification of function connectivity were not observed in the 'sham' control group and the participants who failed to self-regulate the NAcc in the experimental group. Self-regulation was influenced by the baseline motivation.

Conclusions: These findings suggest that the NAcc could be self-regulated using

real-time fMRI neurofeedback and can result in improved motivation in cognitive tasks.

Keywords: Real-time fMRI; nucleus accumbens; motivation; generalization effect; reward

Public Significance Statements

This study applied real-time fMRI-based neurofeedback to volitionally regulate the nucleus accumbens (NAcc). Our findings demonstrated that the NAcc activation could be self-regulated. Importantly, people who successfully learned to self-regulate NAcc activation showed significant improvement in motivation and functional connectivity in the reward circuit. This study demonstrated the potential efficacy of a non-pharmaceutical intervention in alleviating resistant negative symptoms of schizophrenia using real-time fMRI neurofeedback.

Introduction

The nucleus accumbens (NAcc) is widely considered as a brain centre underlying motivation and reward in previous studies (Berridge, 2007; Berridge & Robinson, 1998). The dopaminergic system including the NAcc is associated with incentive salience that attributes value to various rewards and facilitates goal-directed behaviours (Berridge & Robinson, 1998; Wyvell & Berridge, 2000). Other hypothesis and relevant evidence also link the NAcc with hedonic experience (Berridge, 2003; Kringelbach & Berridge, 2009; Wacker, Dillon, & Pizzagalli, 2009), effort-related processes (Salamone, Correa, Farrar, Nunes, & Pardo, 2009), and reward prediction (Schultz, 1998; Schultz, Dayan, & Montague, 1997), which jointly constitute various aspects of motivation and pleasure. Empirical evidence suggests that dysfunction of the NAcc or the ventral striatum in patients with schizophrenia (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Juckel, Schlagenhauf, Koslowski, Wustenberg, et al., 2006; Radua et al., 2015), major depression (Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008; Pizzagalli et al., 2009) and addiction (Beck et al., 2009; Wrase et al., 2007) are associated with negative symptoms, amotivation and anhedonia (Kring & Barch, 2014; Pizzagalli, 2014), which are resistant to treatment with antipsychotics and antidepressants (Kring & Barch, 2014; Pizzagalli, 2014).

Advances in neuroimaging have provided opportunities for alternative non-pharmaceutical interventions to alleviate amotivation and anhedonia. Real-time functional magnetic resonance imaging (rtfMRI) neurofeedback, which is non-invasive and has millimeter spatial resolution (Decharms, 2008; Sulzer, Haller, et

al., 2013), has been successfully applied to self-regulate the activation of the anterior cingulate cortex (Cordes et al., 2015; Mathiak et al., 2015), the amygdala (Paret et al., 2014; Zotev et al., 2011), the dorsal lateral prefrontal cortex (Sherwood, Kane, Weisend, & Parker, 2016; Zhang, Yao, Zhang, Long, & Zhao, 2013), the insula (Lawrence et al., 2014; Sitaram et al., 2014) and the mesolimbic system (Greer, Trujillo, Glover, & Knutson, 2014; Sulzer, Sitaram, et al., 2013). Greer and colleagues (Greer et al., 2014) found that NAcc activation could be self-regulated through rtfMRI-based neurofeedback. However, due to differences in methodology and the lack of understanding of its underlying neurobiology, it is not clear if rtfMRI training could lead to clinically meaningful behavioural changes. In order to develop this technique further and investigate its clinical utility, it is important to understand the neurobiological mechanisms behind self-regulation based on computationally defined learning theories as well as other factors that influence the effectiveness of rtfMRI neurofeedback (Lawrence, et al., 2014). This study aimed to examine individual differences during neurofeedback, and further explored the neurobiological mechanism and generalization effect of real time fMRI neurofeedback training of the NAcc.

As a hub of pleasure experience and reward processing (Berridge, 2007; Kringelbach & Berridge, 2009), the NAcc is engaged in various aspects of motivation. In this study, we employed several cognitive tasks to validate the generalization effect of rtfMRI-based neurofeedback training of NAcc activation, including whether neurofeedback can improve the various aspects of motivation and the reward circuit.

Moreover, the functional connectivity between the NAcc and the ventral medial prefrontal cortex (vmPFC) is implicated in reward processing and pleasure experience (Cauda et al., 2011; Ferenczi et al., 2016; Greer, et al., 2014; Schlaepfer et al., 2008; Wacker, et al., 2009). Volitional regulation of the NAcc has been shown to alter the functional connectivity between the NAcc and the vmPFC during tasks (Greer, et al., 2014). However, no study investigated the task independent functional connectivity changes. Hence we also explored whether the resting state functional connectivity between the NAcc and the vmPFC could be regulated by rtfMRI-based neurofeedback training. The ability to regulate task-free properties of the reward circuit is important for the generalization effect and clinical applications.

The third focus of this study was to find a way to classify individuals into those who are suitable for learning to control their NAcc activation. Although many studies have demonstrated the effectiveness of rtfMRI-based neurofeedback training at the group level, the effectiveness of volitional regulation of target brain areas may be different between different individuals (Sulzer, Haller, et al., 2013). Similar to other pharmacological and non-pharmacological interventions, rtfMRI neurofeedback is unlikely to be a “one size fits all” intervention. Identifying the possible factors that influence the effectiveness of NAcc self-regulation may pave the way for clinical application and personalized intervention.

We hypothesized that NAcc activation could be self-regulated using rtfMRI neurofeedback. We also hypothesized that not all the participants could learn to regulate their NAcc activation and the effectiveness is related to neuropsychological

factors of each participant. Lastly, we hypothesized that participants who were able to self-regulate their NAcc activation equally well would show improved motivation and modified functional connectivity between the NAcc and the vmPFC.

Methods

Participants

Twenty-five healthy female postgraduates were recruited from the University of the Chinese Academy of Sciences in this study. Exclusion criteria included: 1) personal or family history of diagnosable mental disorders; 2) a history of head trauma or encephalopathy; 3) a history of substance abuse; and 4) menstruation in the recent two weeks. The screening of a personal or family history of mental diosrders was confirmed by a semi-structured interview and self-reports. All participants were randomly divided into two groups: the experimental group (N = 20)receiving an actual feedback from the NAcc, and the sham control group (N = 5) receiving a sham feedback from the posterior parahippocampal gyrus. One participant in the experimental group did not complete the imaging protocol, and was subsequently excluded from the study. The Ethics Committees of the corresponding institutions involved in this project approved the study. Informed consent was obtained from all participants.

Procedure

For each participant in both the experimental and control groups, the whole

experiment was conducted in four consecutive days. On the first day, participants were required to complete several questionnaires including the Temporal Experience Pleasure Scale (TEPS) (Chan et al., 2012; Gard, Gard, Kring, & John, 2006), the Behavioral Inhibition System/Behavioral Activation System scale (BIS/BAS) (Carver & White, 1994; Li et al., 2008), the Effort Expenditure for Rewards task (EEfRT) (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009) and the Anticipatory and Consummatory Pleasure task (ACP) (Heerey & Gold, 2007; Lui et al., 2016). The abbreviated Chinese version of the Wechsler Adult Intelligence Scale was used to estimate the IQ of the participants (Gong, 1992). In the morning of the second day, a high-resolution structural magnetic resonance imaging brain scan and a six-minute resting state image were acquired from each participant. In addition, participants were asked to complete three runs of functional Monetary Incentive Delay (MID) task in the scanner (pre-test session). In the afternoon of the second day and the morning of the third day, participants received two five-run sessions of rtfMRI-based neurofeedback training (training *Session 1* and *Session 2*). In the afternoon of the third day, a six-minute resting state image and three runs of functional MID were acquired from each participant (post-test session). Finally, on the fourth day, all participants completed the same questionnaires and behavioural paradigms as the first day (Figure 1(A)). Please refer to the Supplementary Material for details of each questionnaire, and the behavioural and functional imaging paradigms.

Real-time fMRI ROI selection

Before the training *Session 1* and after the pre-test session, the target ROI (Region of Interest) of the bilateral NAcc (size = 65 3x3x3 mm^3 voxels), the sham control target ROI at the bilateral posterior parahippocampal gyrus (size = 746 3x3x3 mm^3 voxels), and the reference ROI at the bilateral lingual cortex (size = 2135 3x3x3 mm^3 voxels) were defined based on the brain structural T1 image of each participant. This was done by inverse-coregistering the predefined ROIs from the Harvard-Oxford atlas with SPM 8 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk)to ensure that the ROI selection was consistent among all participants. The reference ROI was used to control for global brain effect.

Real-time fMRI mental strategies

Each run of both training sessions consisted of five 30-second baseline blocks interleaved with five 30-second regulation blocks, which were administered alternately with a 15-second interval between each block. During the regulation block, they were asked to turn the pointer on a semicircle dashboard to the right (increase), using provided mental strategy "to expect the forthcoming positive events in the future three months". This mental strategy has been applied successfully to regulate the NAcc activations in a previous study (Greer et al., 2014). Participants were also informed that the visual display of the feedback had a delay of 4-5 seconds which was mainly caused by the natural delay of haemodynamic function.

During the baseline block, participants were required to turn the pointer to the left on the feedback screen (decrease). The mental strategy "to do mental arithmetic

such as to minus 3 from 100" was provided in the baseline blocks. The "mental calculation" was a general strategy used during the "baseline/decrease" phase in previous studies (Sulzer, Haller, et al., 2013; Lawrence, et al., 2014). (Figure 1(B)).

Functional imaging paradigm

The functional MID task has been found to be sensitive in detecting the NAcc activation in humans in vivo (Knutson, Fong, Adams, Varner, & Hommer, 2001; Knutson, Westdorp, Kaiser, & Hommer, 2000). In each trial of the MID task, a cue indicated monetary gain, loss or neutral condition was first presented, followed by a blue target which was required to be hit. The duration of each trial was 12 seconds. Participant obtained monetary points if the target was hit in the monetary gain condition, or lost monetary points if the target was missed in the monetary loss condition. Each scan contained three runs of that the task and each run contained nine trials of each condition presented pseudo-randomly. (Please see our previous study, Chan et al., 2016 for details).

Image data acquisition

All participants underwent MRI scans in a Siemens 3T scanner with a 32-channel head coil using a T2* echo planar imaging sequence (TR=2000ms; TE=30ms; FOV=210mm; slices=32; flip angle = 90 degree; image matrix=64×64; voxel dimensions = 3.3 mm ×3.3mm ×4mm) for resting-state, task-based functional MRI and real-time neurofeedback training as well as a high resolution T1 structural brain

image (TR=2300ms; TE=3ms; FOV=256mm; flip angle = 9 degree; image matrix=256 × 256; voxel dimensions = 1mm×1mm ×1mm). Head movement was reduced with a head-holder pad placed between the head coil and the participants' heads.

Real-time fMRI online analysis and neurofeedback

Real-time fMRI data analysis was carried out using a customized pipeline combining SPM, fieldtrip and in-house Matlab scripts as well as the built-in real-time image reconstruction system of the Siemens scanner. Each volume acquired from the scanner was transferred to another workstation computer via network immediately after image reconstruction, and then pre-processed with temporal and spatial corrections. The BOLD signal from the target ROI in the experimental group (or sham ROI in the control group) and reference ROI were extracted in real-time. The visual feedback, i.e. the position of the pointer, on the visually displayed dashboard during the training was calculated with the following formula: Feedback = ROI_{target} ($BOLD_{regulation}$ - $\overline{BOLD}_{baseline}$) – $ROI_{reference}$ ($BOLD_{regulation}$ - $\overline{BOLD}_{baseline}$), where $BOLD_{regulation}$ refers to the BOLD signal from the corresponding ROI of each volume, while $\overline{BOLD}_{baseline}$ refers to the average BOLD signal from the corresponding ROI of the preceding baseline block. The visual feedback was displayed to the participant in the scanner. To minimize fluctuation due to noise from the BOLD signal, the feedback signal was smoothed using a three-point temporal average with weightings set at 0.125, 0.25 and 0.625 for the current and two preceding blocks (Lawrence, et al., 2014). As previously explained, the target ROI of the experimental group was the

NAcc while the target ROI of the sham control group was the posterior parahippocampal gryus. The reference ROI at the lingual cortex and the sham control target ROI were chosen because these areas were normally not engaged in reward processing. They were used to control for non-specific BOLD changes due to other factors such as respiration (Lawrence, et al., 2014).

Offline image data analysis

All the functional images including the rtfMRI-based neurofeedback training data, the functional MID tasks and the resting state data were temporally and spatially corrected for slice timing and motion artifacts. They were then non-linearly normalized to the MNI space (Montreal Neurological Institute). The Friston-24 parameter model regression was adopted to address the head movement measured by the three transition- and three rotation-parameters (Friston, Williams, Howard, Frackowiak, & Turner, 1996; Yan, Craddock, He, & Milham, 2013). All the images were re-sampled into 3x3x3 mm^3 resolution. The rtfMRI-based neurofeedback training data and the functional MID data were smoothed with a Gaussian kernel of 8mm FWHM (full width at half maximum), while the resting state data were smoothed with a Gaussian kernel of 4mm FWHM and detrended to control for slow frequency scanner shift. Data preprocessing of resting state fMRI was carried out using the Dpabi toolbox (http://rfmri.org/DPABI), which integrates functions from SPM, AFNI and FSL.

We then extracted the BOLD signal from both the baseline and regulation blocks

from each voxel of the NAcc. The head movement parameters were regressed from the extracted signals. For each individual data, the residuals obtained from the aforementioned step were averaged among each block from which a 10 (block) * 65 (voxel of the NAcc) matrix was acquired. The conventional whole brain based GLM model was not adopted in this study because the BOLD signal was the feedback we presented, hence the increasing raw BOLD signal was meaningfully interpreted. To classify the participants into the learning and non-learning groups within each of the two training sessions, we inputted the differences between the mean of every regulation block and its preceding baseline block (representing the regulation effect for each block) into a general linear model, and tested whether the regulation effect increased over time. If the beta value was significantly ($p < 0.05$) larger than zero which indicated that the differences were increasing over time with the training runs, we regarded that the participant had successfully learned to control NAcc activation. Otherwise, if NAcc activation did not change over time during the neurofeedback, we classified the participant as non-learner. Based on this criterion, we divided the participants in the experimental group into two subgroups: 1) the *learning group* that successfully learned to control NAcc activation in either or both of the two training sessions; and 2) the *non-learning group* that did not learn to control NAcc in both training sessions. (Please see the Supplementary Table1 and Table2 for more details of this analysis).

Image analysis of the MID task and resting state fMRI data

Three anticipatory cues which corresponded to monetary gain, monetary loss and monetary neutral; six consummatory outcomes which contained monetary gain hit, monetary gain miss, monetary loss hit, monetary loss miss, monetary neutral hit, and monetary neutral miss; and the target hit period of the MID task were modeled into a general linear model. The three parameters of rotation and three parameters of transition were also included in the general linear model as the covariates to control for the head motion. The percentage of signal changes of the monetary gain and monetary loss conditions was then drawn out from the NAcc for group analysis. To confirm the activation of NAcc during the anticipation of monetary gain and loss, small volume correction (SVC) of the NAcc was conducted on the contrasts between [monetary gain > monetary neutral] and [monetary loss > monetary neutral] (Supplementary_Table3). The threshold was set to at $p < 0.05$ with FWE correction. The reaction time during the target hit period for the three different anticipatory conditions was also calculated as the behavioural measure of motivation.

Functional connectivity defined by the Z-transformation of the correlation coefficient between the NAcc and the vmPFC was calculated based on the resting state fMRI image. We also constructed an a-priori reward circuit based on previous studies (Haber & Knutson, 2010; Kringelbach & Berridge, 2009; Pizzagalli, 2014) with connectivity comprising a total of 28 regions (the bilateral substantia nigra, the bilateral NAcc, the bilateral putamen, the bilateral caudate, the bilateral thalamus, the bilateral amygdala, the bilateral insula, the bilateral lateral globus pallidus, the bilateral medial globus pallidus, the bilateral DLPFC, the bilateral vmPFC, bilateral

inferior OFC, the bilateral middle OFC, and the bilateral superior OFC). The regions of interest (ROI) adopted in this study were obtained from the AAL atlas (Tzourio-Mazoyer et al., 2002). In the dataset for each participant, a correlation matrix was constructed from the time series correlation of each ROI. In network theory (Watts & Strogatz, 1998), C_p denotes the average clustering coefficients across all the nodes, while L_p denotes the average shortest path length between each pair of nodes. The C_p and L_p of the reward circuit were compared with 100 random networks. A small world would be featured with the following conditions: $\gamma = C_p^{real}/C_p^{rand} > 1$, $\lambda = L_p^{real}/L_p^{rand} \sim 1$ and $\sigma = \gamma/\lambda > 1$. The small world properties of the reward circuit were calculated based on sparsity ranging from 0.1 to 0.4 with a 0.01 step length in the toolbox GRETNA (http://www.nitrc.org/projects/gretna/). We did not perform global signal regression on the resting state functional image due to the ongoing debate on its reliability (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009; Saad et al., 2012).

Statistical tests

Using SPSS 18, we first compared the demographics, baseline motivation and functional connectivity of the experimental group with the sham control using the Mann-Whitney U test. Then the changes observed in the behavioiural tests before and after rtfMRI training were compared using the Wilcoxon Signed Ranks test in both the experimental and the sham control groups. These tests included self-reported questionnaires, behavioural performances, e.g. reaction time and NAcc

activation in the MID task, functional connectivity between the NAcc and the vmPFC and small-world properties of the reward circuit. Finally, the same non-parametric tests were used to compare the corresponding changes before and after the neurofeedback training between the *learning* and the *non-learning groups*.

Results

Training effect

Nine participants in training *Session 1* and 10 participants in training *Session 2* in the experimental group successfully learned to self-regulate their NAcc activation (Figure 2). Over 14 participants (73.68%) in the experimental group successfully learned to self-regulate their NAcc activation in at least one training session. The remaining 5 participants who failed to regulate NAcc activation in both sessions from the experimental group were classified into the *non-learning group*. The training effect of each participant is reported in Supplementary_Table1. In the sham control group, three participants in training *Session 1* and one participant in training *Session 2* successfully learned to regulate posterior parahippocampal activation. Only one participant learned to self-regulate the NAcc activation in both *Session 1* and *Session 2* (Supplementary_Table1 and Supplementary_Table2).

Generalization effect

There was no significant difference between the experimental group and the sham control group in baseline demographics and motivation behavioural

performance. At baseline, we found no significant group difference in functional connectivity between the NAcc and the vmPFC, except that the experimental group showed significantly lower press rates to avoid undesirable pictures in the ACP task (Table 1). In the experimental group, the press rate to seek desirable pictures (p = 0.009, Cohen's d = -0.43) and to avoid undesirable pictures (p = 0.003, Cohen's d = -0.85) were both increased after the rtfMRI-based neurofeedback training. Furthermore, their reaction time to hit the target in the MID task was decreased during the anticipation of monetary gain (p = 0.002, Cohen's d = 0.79) and monetary loss (p = 0.003, Cohen's d = 0.77). The experimental group showed significantly decreased functional connectivity between the left NAcc and the left vmPFC (p = 0.011, Cohen's d = 0.89) and the right vmPFC (p = 0.033, Cohen's d = 0.73), and between the right NAcc and the right vmPFC (p = 0.033, Cohen's d = 0.72) (Table 1). However, no improvement in performance in behavioural tasks and no change in functional connectivity were observed in the sham control group. Both the experimental and sham control groups failed to show significant changes on the EEfRT task and small world properties of the reward circuit before and after training (Table 1&Figure 3).

Individual differences in neurofeedback

To explore which personality and neurophysiological trait predicted the effectiveness of neurofeedback training, we compared the baseline variables of the *non-learning group* (N = 5)with the *learning group* (N = 14). The two groups were not

significantly different in demographics (Table 2). We found that the *learning group* showed significantly higher Drive score on the BAS (p = 0.028, Cohen's d = -1.43). Participants in the *learning group* were more likely to choose a hard task in the middle (p = 0.013, Cohen's d = -1.17) and high (p = 0.015, Cohen's d = -1.03) reward disparity of the EEfRT task compared with the *non-learning group*. In addition, the *learning group* also showed a trend in having higher NAcc activation during the anticipation of monetary gain in the MID task (p = 0.052, Cohen's d = -1.18) (Table 2).

Compared with the *non-learning group*, the *learning group* showed increased press rate to seek desirable pictures (p = 0.005, Cohen's d = -0.96) and to avoid undesirable pictures (p = 0.002, Cohen's d = -0.58) in the ACP task, and reduced reaction time to hit the target in the MID task during the anticipation of monetary gain (p = 0.019, Cohen's d = 0.89) and monetary loss (p = 0.005, Cohen's d = 1.1) after rtfMRI-based neurofeedback training. Moreover, the *learning group* showed significantly decreased functional connectivity between the left NAcc and the left vmPFC (p = 0.013, Cohen's d = 1.12) and the right vmPFC (p = 0.035, Cohen's d = 0.89), and there was a decrease in functional connectivity between the right NAcc and the right vmPFC with trend significance (p = 0.064, Cohen's d = 0.73) (Table 2). The small world properties of the reward circuit in the *learning group* were also increased with sparsity ranging from 0.21 to 0.4 after the whole training (Figure 3). Changes in behavioural performance, functional connectivity and small world properties of the reward circuit were not observed in the *non-learning group* (Table 2&Figure 3).

Discussion

In this study, we found that activity of the NAcc could be self-regulated through rtfMRI-based neurofeedback training. Increased motivation measured by behavioural and functional imaging paradigms, and decreased functional connectivity between the NAcc and the vmPFC were observed in the experimental group, but not in the sham control group, after two sessions of training on self-regulation of the NAcc. As expected, not all participants were capable of learning to control NAcc activation after two training sessions in our study. Participants who successfully learned to regulate their NAcc had higher trait motivation than non-learning participants.

Self-regulation of the NAcc was achieved by the rtfMRI-based neurofeedback training in this study, which corroborated with previous findings (Greer, et al., 2014; Kirsch, Gruber, Ruf, Kiefer, & Kirsch, 2016; MacInnes, Dickerson, Chen, & Adcock, 2016), suggesting that rtfMRI feedback technology could not only mediate the activation of superficial cortical areas (Sherwood, et al., 2016; Zhang, et al., 2013), but also deep subcortical structures in the mesolimbic system (Greer, et al., 2014; Sulzer, Sitaram, et al., 2013). Empirical evidence has suggested that NAcc activation is associated with the anticipation of rewarding stimuli (Knutson, Fong, Adams, Varner, & Hommer, 2001; Knutson & Gibbs, 2007; Knutson, Westdorp, Kaiser, & Hommer, 2000). It has been argued that the ability to anticipant future rewards such as positive events can activate the NAcc, thus increasing the activity in the NAcc using neurofeedback training (Greer, et al., 2014) may improve anhedonia (Favrod, Giuliani, Ernst, & Bonsack, 2010; Nguyen et al., 2016). The multiple-session training strategy

adopted in this study is different from previous similar studies on rtfMRI-based neurofeedback training on the NAcc (Greer et al., 2014; Kirsch et al., 2016; MacInnes et al.,, 2016). The longer length of training could increase the likelihood of acquiring NAcc self-regulation in our participants.

Most importantly, we found a generalization effect of the rtfMRI-based neurofeedback training which was less robust. After two rtfMRI-based neurofeedback training sessions, the *learning group* showed accelerated response to acquire desirable affective pictures or to avoid undesirable affective pictures during the anticipatory phase of the ACP task, and faster reaction time during the anticipation of monetary gain or loss in the MID task. Taken together, our results provide empirical evidence supporting the potential use of rtfMRI-based neurofeedback training in the intervention of refractory negative symptoms such as amotivation and anhedonia.

Participants in the experimental group, who successfully learned to regulate the NAcc, showed weakened functional connectivity between the NAcc and the vmPFC, both of which is engaged in reward processing and pleasure experience (Cauda, et al., 2011; Wacker, et al., 2009). Consistent with our findings, Schlaepfer, et al. (2008) found a significant decrease in activation in the vmPFC after deep brain stimulation at the NAcc in patients with major depression. In addition, Ferenczi, et al. (2016) used optogenetic fMRI to manipulate the brainwide neural activity of rats, and found that increases in mPFC activity reduced dopaminergic activity in the NAcc and relevant behavioural drive for dopaminergic stimulation. This suggests that inhibitory

projections from the vmPFC to the NAcc can be altered by regulating NAcc activity in both humans and animals, and this neural mechanism may underlie our findings of reduced functional connectivity between the vmPFC and the NAcc. In a previous resting-state fMRI study, patients with first-episode schizophrenia exhibited hyper-connectivity between vmPFC and NAcc (Fornito et al., 2013). The rtfMRI-based neurofeedback training on NAcc activation may provide a potential non-invasive intervention to normalize this hyper-connectivity in schizophrenia. However, we should interpret these findings cautiously due to the relatively small sample size in the shame control group. Although the pre- and post-training comparisons on functional connectivity in the sham control group was not significant, the effect sizes were close to what we found in the experimental group. Future studies recruiting a larger sample size of sham control should be conducted to replicate and extend our findings.

We also observed improvements in the network properties of the reward circuitry after rtfMRI-based neurofeedback training in the *learning group*. The increased small world property γ and σ of the reward circuity in the *learning group* suggests that the reward circuit had become more efficient in information processing after the training. The disrupted reward network and the ventral striatal dopaminergic system play a vital role in amotivation and anhedonia in schizophrenia and major depression (Kring & Barch, 2014; Pizzagalli, 2014; Radua, et al., 2015). Improving the small world properties of the reward circuit in these patients using rtfMRI neurofeedback may have potential treatment benefits.

About 70 % of the participants in the experimental group successfully learned to self-regulate their NAcc using rtfMRI-based neurofeedback after only two training sessions. The *learning group* showed higher BAS drive score, higher tendency to select high rewarding choices and higher NAcc activation during the anticipation of monetary rewards compared with the *non-learning group*. The *learning group* also showed higher baseline motivation than the *non-learning group*, suggesting the importance of motivation in predicting the effectiveness of rtfMRI-based neurofeedback training (Sokunbi, Linden, Habes, Johnston, & Ihssen, 2014).

To translate rtfMRI-based neurofeedback training to clinical practice, a personalized intervention plan that maximize its efficacy is crucial. Furthermore, the appropriate dosage of rtfMRI-based neurofeedback training requires further investigation (Sulzer, Haller, et al., 2013). It is interesting to note that some participants who successfully learned self-regulation in the first training session failed in the second session in our study. This suggests that one-session training may not be sufficient to achieve and maintain the training effect, and multiple sessions of training with appropriate intervals may be necessary to establish a stable training effect. A longer but optimal training time may contribute to the significant behavioural and brain changes after the rtfMRI neurofeedback.

The limited sample size of the sham control group means that the non-regulation results should be treated with caution. However, the specificity of rtfMRI training on the NAcc and the ventral striatum have been well established in the literature (Greer, et al., 2014; Kirsch, et al., 2016; MacInnes, et al., 2016). It

should also be noted that the sample size of both the experimental and sham control groups in this study was comparable to most other similar studies in the extant literature (Chiew, LaConte, & Graham, 2012; Ruiz, Buyukturkoglu, Rana, Birbaumer, & Sitaram, 2014). The other limitation was the potential gender bias in this study. Although there is no reported gender difference in real-time neurofeedback training, some evidence has suggested that gender difference on the pleasure experience, memory and beliefs may be associated with NAcc activation (Kim-Prieto, Diener, Tamir, Scollon, & Diener, 2005; Robinson & Clore, 2002). Thus, to avoid the influence of gender difference, we included only female participants in this study. It is unclear whether rtfMRI neurofeedback is equally efficacious in males. Finally, the present study only examined the short-term effect of self-regulation of NAcc through rtfMRI-based neurofeedback training. Future study should examine the generalization effect by recruiting more ecological-valid measures to evaluate its effect over a longer period.

CONCLUSION

Activation of the NAcc could be volitionally regulated using rtfMRI-based neurofeedback training in healthy people. Baseline motivation may influence its effectiveness. People who were successful in learning self-regulation had higher baseline motivation than those who did not acquire the skill. Real-time neurofeedback training on the NAcc may be able to improve behavioural manifestations of motivation and modify the reward circuit. This technique may have

clinical potential for alleviating amotivation and anhedonia in patients with schizophrenia and other related disorders.

CONFLICTS OF INTEREST

None to be declared.

Legends

Figure 1. The experimental procedure and real-time fMRI neurofeedback training system (A) The procedure of whole experiment, TEPS = Temporal Experience Pleasure Scale, BAS = Behavioral Activation System, BIS = Behavioral Inhibition System, ACP =Anticipatory and Consummatory Pleasure task, EEfRT = Effort Expenditure of Reward Task, T1 = Structural image, MID = Monetary Incentive Delay task, REST = Resting-state functional image; (B) The real-time activation of the nucleus accubmens was drew out and processed on-line, then the calculated value was presented on a dashboard. Participants were required to control the pointer on the dashboard through the difference strategies during the baseline and training blocks.

Figure 2. The real-time fMRI training on the self-regulation of nucleus accumbens activation The X-axis denotes the runs and the Y-axis denotes the BOLD difference in NAcc between the training block with the previous baseline block.

Figure 3. The difference before and after the real-time fMRI training on the small-world properties γ and σ of the reward circuit The X-axis denotes the different sparsity of the network, while the Y-axis denotes the values of γ or σ. The *learning group* showed improved small-world properties γ and σ of the reward circuit after the real-time fMRI self-regulation on the NAcc activation that was absent in the non-learning and sham control groups.

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