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Anhedonia correlates with functional connectivity of the nucleus accumbens subregions in patients with major depressive disorder

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ABSTRACT

Background: The nucleus accumbens (NAc) is an important region in reward circuit that has been linked with anhedonia, which is a characteristic symptom of major depressive disorder (MDD). However, the relationship between the functional connectivity of the NAc subregions and anhedonia in MDD patients remains unclear.
Methods: We acquired resting-state functional magnetic resonance imaging (fMRI) scans from fifty-one subjects (23 MDD patients and 28 healthy controls). We assessed subjects' trait anhedonia with the Temporal Experience of Pleasure Scale (TEPS). Seed-based resting-state functional connectivity (rsFC) was conducted for each of the NAc subregions (bilateral core-like and shell-like subdivisions) separately to identify regions whose rsFCs with the NAc subregions were altered in the MDD patients and regions whose rsFCs with the NAc subregions showed different correlates with anhedonia between the MDD patients and the healthy controls.
Results: Compared with the health controls, the MDD patients showed decreased rsFCs of the right NAc core-like subdivision with the left mid-anterior orbital prefrontal cortex and the right inferior parietal lobe as well as decreased rsFC of the left NAc core-like subdivision with the right middle frontal gyrus. Moreover, the severity of anhedonia by the group interaction was significant for the rsFC of the right NAc shell-like subdivision with the subgenual/pregenual anterior cingulate cortex and the rsFC of the right NAc core-like subdivision with the precuneus.
Conclusions: We found that the neural correlates of anhedonia indicated by the rsFCs of the NAc subregions were modulated by depression. The modulation effect was regionally-dependent. These findings enrich our understanding of the neural basis of anhedonia in MDD.

1. Introduction

Anhedonia refers to the inability to experience pleasure in all or almost all activities, which is a core symptom of major depressive disorder (MDD) (Association, 2013). Anhedonia has been described as an endophenotypic marker and as a risk factor for MDD (Cao et al., 2019; Hasler et al., 2004; Treadway and Zald, 2011). Anhedonia is a predictor of increased risk of death and disability due to MDD. Moreover, the presence of anhedonia is linked to worse treatment outcomes for MDD patients, such as poorer recovery of psychosocial functioning and longer time to remission (Covinsky et al., 2014; Gong et al., 2018; McMakin et al., 2012; Vinckier et al., 2017). It has been hypothesized that individual symptoms in MDD are more likely than diagnostic categories to be linked with specific biological components (Clark et al., 2017; Der-Avakian and Markou, 2012). Therefore, elucidating the neural basis of anhedonia is both necessary and important in understanding the pathophysiology of MDD.

Anhedonia reflects the deficits in the processing of reward information because the capacity to feel pleasure is critical for processing rewards (Der-Avakian and Markou, 2012; Hoflich et al., 2019; Rizvi et al., 2016). Anhedonia could be categorized into anticipatory anhedonia and consummatory anhedonia (Berridge and Robinson, 2003; Gilbert and Wilson, 2007; Schultz, 2002). The anticipatory pleasure (or 'wanting') is related to positive anticipation of future events and gaining

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pleasure from a positive prediction (Gard et al., 2006; Wu et al., 2017). The consummatory pleasure (or 'liking') is related to the in-the-moment experience of pleasure (Gard et al., 2006; Sherdell et al., 2012; Wu et al., 2017). Previous studies suggest that the two types of anhedonia are differentially affected by MDD. For example, researchers found MDD patients display a lower level of anticipatory pleasure in comparison to consummatory pleasure as well as an elevated level of anticipatory displeasure relative to consummatory displeasure (Hallford et al., 2020; Wu et al., 2017).

Neuroimaging studies have demonstrated that the nucleus accumbens (NAc) is well-recognized as a center of reward processing and is a hotspot in hedonic circuits (Baler and Volkow, 2006; Berridge and Kringelbach, 2008; Knutson et al., 2007). The NAc has extensive interconnections with other regions of the limbic system and the prefrontal cortex. In addition, it is involved in complex, reciprocal interactions with dopaminergic, serotoninergic and glutamatergic systems (Abdallah et al., 2017; Sturm et al., 2003; Young et al., 2016). Animal studies have found that the NAc is important to the hedonic perception of rewards and it is also in charge of regulating affective responses to rewards (Berridge and Kringelbach, 2008; Faure et al., 2010; Kelley et al., 2002). Importantly, converging neuroimaging evidence suggests that the dysfunction of the NAc is related to the anhedonia. In healthy controls (HC), anhedonia was negatively correlated with the volume of NAc (Wacker et al., 2009) and negatively correlated with the activation of the NAc induced by musical stimuli (Keller et al., 2013). In patients with MDD, neuroimaging has repeatedly provided evidence for the role of the NAc in anhedonia. For example, the NAc had weaker responses during the anticipation of the reward in a money incentive delay task among the MDD patiens (Green et al., 2019; Pizzagalli et al., 2009). In addition, the NAc also showed less activation induced by musical stimuli (Jenkins et al., 2018) and greater anhedonia was associated with weaker functional connectivity between the NAc and the posterior ventromedial prefrontal cortex during music listening in MDD patients compared to the HC (Young et al., 2016). Furthermore, a recent study suggests that the life-time MDD patients have smaller NAc volumes (Ancelin et al., 2019). However, most of these studies focus on the task-induced brain activity or structural brain alterations.

Resting-state functional magnetic resonance imaging (rsfMRI) is a powerful tool to investigate the intrinsic activity and connectivity within brain circuits at the resting state (Dichter et al., 2015; Keilholz et al., 2017; Van Dijk et al., 2010). Additionally, rsfMRI is often used to draw inferences about individual differences in behavioral traits or cognitive functions as well as differences between healthy and diseased populations (Bhaumik et al., 2017; Gao et al., 2018; Geerligs et al., 2015; Smith et al., 2009; Zheng et al., 2019). Many efforts have been made to identify the abnormality in the resting-state functional connectivity (rsFC) in MDD (Dichter et al., 2015; Kaiser et al., 2015), including how the abnormal rsFC is related to the NAc (Gong et al., 2018). For example, patients with MDD showed decreased rsFC of the NAc with the rostral anterior cingulate (Janes et al., 2018). In addition, adolescents with MDD showed reduced rsFC between the NAc and the middle temporal gyrus (Gabbay et al., 2013). More importantly, a correlation between anhedonia and the rsFC of the NAc with the anterior cingulate cortex (ACC), including the subgenual ACC (sgACC) and pregenual ACC (pgACC), as well as the caudate was reported in the adolescents with MDD (Gabbay et al., 2013). However, there are still lack of studies on the association of the brain functional connectivity of the NAc with anhedonia in MDD patients at the resting state.

The NAc is a heterogeneous brain region that can be divided into core-like and shell-like subdivisions both in animal and human studies (Xia et al., 2017; Zahm and Brog, 1992). The core-like subdivision is located in the dorsolateral NAc, which has prominent cortical connections with the lateral orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), amygdala, thalamus, substantia nigra and other subcortical structures (Zahm, 2000; Zahm and Brog, 1992). This core-like subdivision is associated with goal-directed behavior, instrumental learning, and motivation. It plays a role in selectively instigating an approach toward an incentive stimulus that is associated with the best available reward (Bessa et al., 2013; Xia et al., 2017). The shell-like subdivision is located in the ventromedial NAc, which has intensive connections with regions in the mediocaudal prefrontal cortex (such as the medial prefrontal cortex (MPFC), medial OFC and subcallosal cortex), limbic regions (such as the hippocampus and amygdala), ventral tegmental area and other subcortical structures (Zahm, 2000; Zahm and Brog, 1992). The shell-like subdivision is associated with integrating motivational valence and novelty, and thus plays a role in suppressing lesser or non-reward stimuli that may obstruct with the best reward predicting stimuli (Bessa et al., 2013; Xia et al., 2017). Recent studies also suggest that the NAc core-like and shell-like subdivisions are involved in aversion (Castro et al., 2016; Yamaguchi et al., 2015) and reward processing (Castro and Berridge, 2014; Pecina and Berridge, 2005), respectively. The functional differences between the NAc core-like and shell-like subdivisions may be associated with their distinct regulation of dopamine release (Goto and Grace, 2008). Reduced dopaminergic firing in different NAc subregions might in turn, be associated with different anhedonia phases in MDD patients (Gorwood, 2008). Both animal and human studies have also suggested that anticipatory anhedonia is mediated by the NAc core-like subdivision and that consummatory anhedonia is mediated by the NAc shell-like subdivision (Berridge and Kringelbach, 2015; Berridge and Robinson, 2003; Saddoris et al., 2015; Zisner and Beauchaine, 2016). Clinical studies have shown that deep brain stimulation in the NAc shell-like and core-like subdivisions might improve the effects of antianhedonics and antidepressants, respectively (Bewernick et al., 2010, 2012). Taken together, these evidences suggest that the NAc core-like subdivision and the shell-like subdivision play different roles in anhedonia. However, it is unclear whether the different NAc subregions show distinct functional connectivity profiles with anhedonia in MDD patients.

In this study, we aimed to investigate the relationship between the rsFC of the NAc subregions and anhedonia in MDD patients. We hypothesized that MDD patients show altered rsFC of the NAc subregions compared to HC. In addition, we hypothesized that MDD patients differ from HC in the correlations between the rsFC of the NAc subregions and anhedonia because the capacity to experience pleasure differs among individuals and the diagnosis of depression may modulate this neural correlate of anhedonia. More importantly, the regionally-dependent modulation in the correlations between the rsFC of the NAc subregions and anhedonia may exist. Previous studies have found that deficits in many regions in the prefrontal cortices (PFC), such as the OFC, ventromedial prefrontal cortex (vMPFC) and dorsolateral PFC, have been implicated in anhedonia (Berridge and Kringelbach, 2008; Der-Avakian and Markou, 2012; Hoflich et al., 2019; Yang et al., 2017b) and these prefrontal cortices have intensive connections with the previously mentioned NAc subregions (Xia et al., 2017). Therefore, we speculated that the regionally-dependent changes in the rsFC of the NAc subregions and the regionally-dependent modulation in the correlations between the rsFC of the NAc subregions and anhedonia may be found in the prefrontal cortices.

2. Materials and Methods

2.1. Participants

The study was comprised of 23 MDD outpatients and 28 HC. The MDD patients were recruited from the Beijing Anding Hospital of the Capital Medical University. The HC were recruited via advertisements as a control group. This study was approved by the Institutional Review Boards of Beijing Anding Hospital, Capital Medical University, and the Institute of Psychology, Chinese Academy of Sciences. All subjects have proceeded written informed consents.

The MDD patients were diagnosed by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for a major

depressive episode. All MDD patients met the following criteria: (1) the diagnosis was confirmed by the Structured Clinical Interview for the DSM-IV (SCID); (2) right-handed; (3) age in the range of 18 to 45 years old. The MDD patients were excluded if they had any preexisting or concurrent co-morbid primary diagnoses that met the DSM-IV criteria for any Axis I disorder other than MDD, such as schizophrenia or alcohol/substance use disorders. Additional exclusion criteria were depression with psychotic symptoms, acutely suicidal or homicidal behavior, a history of mania or hypomania, a history of trauma resulting in a loss of consciousness, a history of major neurological or physical disorders that could lead to an altered mental state, or current pregnancy or breastfeeding. In addition, none of the patients had received electro-convulsive therapy in six months prior to the study.

Eight MDD subjects had the first depressive episode whose symptoms had been controlled after antidepressant treatments when they were recruited. The other MDD patients had at least two depressive episodes. The mean number of depressive episodes prior to this study was 2.35 (SD = 1.37) times. The mean age-of-onset of depressive episodes was 25.87 (SD = 7.24) years old. In the MDD group, all of the patients received antidepressant medications (SSRIs and/or SNRIs), except for one who did not take any psychotropic medications. Additionally, one patient was also taking low-dose benzodiazepines.

The HC were free of any known psychiatric conditions and had never taken any form of antidepressant medications, which was screened by a self-report questionnaire. Additional exclusion criteria adopted for the HC were the same as those for the MDD group. All subjects had no contraindications to MRI scanning, such as cardiac or pulmonary disease that could influence the blood-oxygen-level dependent (BOLD) response. The demographic and clinical information of the subjects are presented in Table 1.

2.2. Behavioral assessment

All of the subjects received clinical and behavioral examinations. Anhedonia was assessed by the Chinese version of the Temporal Experience of Pleasure Scale (TEPS) (Chan et al., 2012), which has been validated and widely used in the Chinese population (Yang et al., 2017a; Zhou et al., 2019). The TEPS scale contains two dimensions: anticipatory pleasure (TEPS anticipatory) and consummatory pleasure (TEPS consummatory) (Chan et al., 2012). A lower total score indicates higher level of anhedonia, i.e., lower level of pleasure. Depression severity was assessed by the 17-item Hamilton Rating Scale for Depression (HAMD-17). Anxiety levels were assessed by the Hamilton Anxiety Rating Scale (HAMA).

2.3. Image acquisition

We conducted functional magnetic resonance imaging (fMRI) scans to all subjects with GE Discovery MR750 3.0 Tesla scanner at the Magnetic Resonance Imaging Research Center, Institute of Psychology, Chinese Academy of Sciences. High-resolution structural 3D T1-weighted images were acquired by the gradient recalled echo sequence with the following parameters: TI = 450 ms, receiver bandwidth = 31.25, matrix = 256 × 256, field of view (FOV) = 240 mm, slice thickness = 1.5 mm, and flip angle = 12°. Resting-state functional MRI images were obtained using a gradient-recall echo-planar imaging (GRE-EPI) pulse sequence with the following parameters: repetition time = 2000 ms, echo time = 30 ms, FOV = 220 mm × 220 mm, matrix = 64 × 64, flip angle = 70°, number of slices = 33, and slice thickness = 4 mm with no gap. During the fMRI scanning, all of the subjects were required to stay awake with their eyes closed, relax their minds and keep their bodies still. Each functional run lasted for 10 min.

Table 1
Demographic and clinical characteristics.

Characteristics	MDD (N = 23)	HC (N = 28)	P Value
Gender (male/female)	13/10	16/12	0.96[a]
Age (years)	31.22 ± 5.7	29.57 ± 5.8	0.32[b]
Education (years)	14.91 ± 3.22	15.25 ± 2.55	0.68[b]
Mean FD (mm)	0.11 ± 0.04	0.13 ± 0.05	0.16[b]
HAMD-17	13.13 ± 6.96	0.89 ± 1.73	0.000[b]
HAMA	9.83 ± 6.86	0.64 ± 1.16	0.000[b]
TEPS	70.48 ± 16.37	83.14 ± 11.64	0.002[b]
Anticipatory	29.52 ± 7.47	36.61 ± 5.6	0.000[b]
Consummatory	39.83 ± 9.68	46.54 ± 6.99	0.006[b]

Abbreviation: MDD, major depression disorder; HC, health control; FD, frame-wise displacement; HAMD-17, 17-item Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; TEPS, Temporal Experience of Pleasure Scale; a, Chi-squared test; b, two sample *t*-test.

2.4. Functional imaging data preprocessing

Neuroimaging data were processed by the Data Processing & Analysis for (Resting-State) Brain Imaging (Yan et al., 2016) (DPABI v4.3, http://rfmri.org/DPABI). For each of the subjects' data, the first five time points were discarded for stabilization of the MR signal. After realignment, we co-registered the unified segmentation of the T1 images to the mean functional image using a six degrees-of-freedom linear transformation without resampling. Then, the time course for covariates, including 24 motion parameters, 5 principal components from the individual segmented cerebrospinal fluid and white matter regions (Behzadi et al., 2007), and linear and quadratic trends (Yan et al., 2013), were regressed out to avoid the potential impact of physiological artifacts. Here, the head motion was regressed out using the Friston 24-parameter model (6 head motion parameters, 6 head motion parameters from one time point before, and the 12 corresponding squared items) (Friston et al., 1996). The remaining images were standardized by the Montreal Neurological Institute (MNI) template, re-sampled to 2 × 2 × 2 mm^3 voxels, and spatially smoothed using 4 mm full width at half maximum (FWHM). The smoothed data were filtered using a band-pass filter (0.01–0.1 Hz) to eliminate low-frequency and high-frequency noises. In addition, a volume-based framewise displacement (FD) was computed based on their realignment parameters to quantify head motion (Power et al., 2012). In addition, the mean FD was calculated by the average of the volume-based FD time series (Patel et al., 2014; Power et al., 2012).

2.5. Functional connectivity and statistical analysis

Seed-based rsFC was calculated using the DPABI software. The subregions of the NAc from a recent 2-cluster solution with shell-like and core-like subdivisions (Xia et al., 2017) were used as the seeds. This resulted in four seed regions for the rsFC analysis (the left core-like subdivision, the right core-like subdivision, the left shell-like subdivision and the right shell-like subdivision). By averaging the time series of all of the voxels within each seed region, the mean time series of each seed region was acquired. A Pearson correlation analysis was conducted between the mean time series of the seed region and time series of each voxel of the whole brain. Fisher's r-to-z transformation was applied to convert the correlation coefficient map into the z-map to improve the normality. In this way, individual functional connectivity maps were obtained.

In order to validate the parcellation of the NAc subregions, the connectivity maps of each seed region were first submitted to one sample *t*-tests to identify regions showing significant connectivity with the four NAc subregions within the HC group and the MDD group, respectively (voxel-wise $p < 0.001$; cluster-level family-wise error (FWE) $p < 0.05$). Then, paired-samples *t*-tests were conducted to investigate the differences in rsFCs between the left NAc core-like and the left shell-like subdivisions and between the right NAc core-like and the right shell-like subdivisions in the whole sample (voxel-wise $p < 0.001$; cluster-level

FWE $p < 0.05$).

To investigate the effects of group, anhedonia and their interaction on the rsFC of the NAc subregions, 8 separate second-level multiple regression analyses were performed. Each of functional connectivity maps of NAc subregions was separately entered into the multiple regression model as the independent variable, and TEPS consummatory or anticipatory scores, group, and group*TEPS consummatory or anticipatory were entered as covariates of interest, while controlling for gender, age, education and mean FD value. Before this analysis, the multicollinearity between the group and TEPS scores was tested by Spearman's rank correlation method. Moderate correlations between the group status and the TEPS consummatory score ($r = -0.35, p = 0.01$) and TEPS anticipatory score ($r = -0.47$, $p = 0.001$) were found. Based on the criteria that the correlation coefficients of more than 0.7 indicates a collinearity between variables (Dormann et al., 2013), this study showed an acceptable multicollinearity between focal variables, and thus we conducted the followed multiple regression analysis for each type of anhedonia score separately. The significant results in each regression analyses were reported at a threshold of a cluster-level FWE corrected p-value of 0.05 (individual voxel height threshold of $p < 0.001$). If an interaction effect was present, a simple effect analysis was conducted to estimate the interaction effect using MODPROBE, which is an aide for probing single-degree-of-freedom interactions in linear regression analyses with SPSS version 24 (Hayes and Matthes, 2009; Zhou et al., 2014). A linear regression with "Enter" method was conducted to calculate the values of variance inflation factor (VIF), which was used to verify the multicollinearity between MDD status and anhedonia. If the VIF values were less than 5, the variables had acceptable multicollinearity (Akinwande et al., 2015).

Two-sample t-test and Chi-squared test were used to compare the differences of demographic data and clinical variables between the MDD and the HC groups.

3. Results

3.1. Demographic and clinical information

As shown in Table 1, there were no significant differences in the age, gender or education levels ($p > 0.05$) of the participants in the MDD and the HC group. The MDD patients showed higher scores on the HAMD and the HAMA compared to the subjects in the HC group. Furthermore, the MDD patients had lower mean scores on the TEPS as well as on the anticipatory and consummatory subscales compared to the HC group ($p < 0.01$), indicating the MDD patients had more severe anhedonia in both anticipatory and consummatory pleasure.

3.2. RSFC analyses of each NAc subregion

One sample t-test analyses showed that the positive rsFCs with the four NAc subregions were concentrated in the frontal gyrus, anterior cingulate cortex, caudate, subcallosal gyrus, thalamus, orbitofrontal cortex, hippocampus, and parahippocampal gyrus in both the MDD group and the HC group. The negative rsFCs were mainly distributed in the inferior parietal lobules in the HC group; however, no significant negative rsFCs were found in the MDD patients (Fig. 1). The rsFCs pattern of each NAc subregion in the HC group was consistent with previous studies (Wang et al., 2019; Xia et al., 2017). Then, the paired sample t-test analyses revealed that the NAc core-like subdivision showed stronger rsFCs with the regions of frontal lobe, anterior cingulate and inferior parietal lobule as well as weaker rsFCs with the regions of the subcallosal gyrus, hippocampus, and parahippocampus gyrus compared with the NAc shell-like subdivision (Fig. 2). These differences in rsFCs between the NAc core-like subdivision and shell-like subdivision were also consistent with previous studies (Wang et al., 2019; Xia et al., 2017).

3.3. Effects of group, anhedonia and their interaction on rsFC of the NAc subregions

3.3.1. The effect of anticipatory anhedonia, diagnosis and their interaction

Through the multiple regression model with each functional connectivity maps of NAc subregion as input separately, and TEPS anticipatory score, group, and group* TEPS anticipatory as covariates of interest, we found a significant main effect of anticipatory anhedonia on the rsFC of the right NAc core-like subdivision with the vermis of the cerebellum (FWE corrected $p = 0.001$).

There was no significant effect of group or group*TEPS anticipatory on the rsFC of NAc subregions (Table 2).

3.3.2. The effect of consummatory anhedonia, diagnosis and their interaction

Through the multiple regression model with each functional

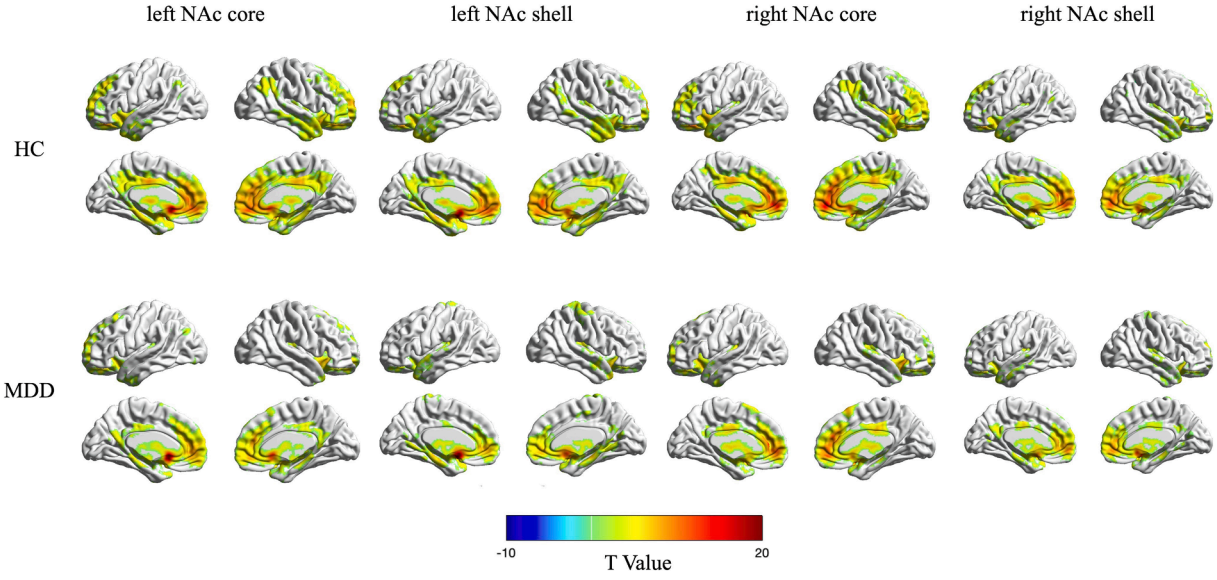

Fig. 1. Spatial distributions of the rsFCs of the four NAc subregions within the HC group and the MDD patients. The spatial distributions of the rsFCs were projected onto a surface brain using BrainNet Viewer (https://www.nitrc.org/projects/bnv/).

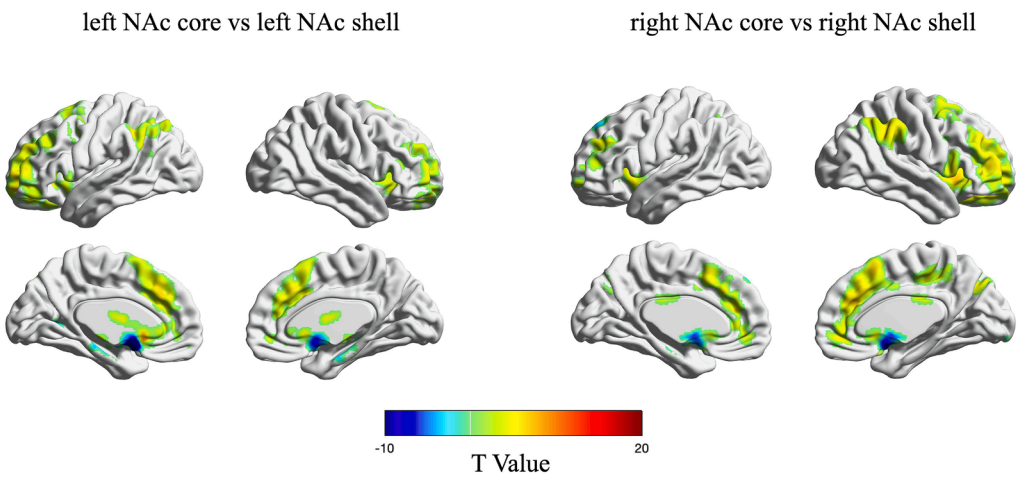

Fig. 2. Regions showing significant differences in rsFCs with the NAc core-like subdivision compared with the NAc shell-like subdivision across the participants. Warm colors represent the regions showing greater rsFCs with the NAc core-like subdivision compared with the NAc shell-like subdivision. Cool colors represent the regions showing greater rsFCs with the NAc shell-like subdivision compared with the NAc core-like subdivision. The images were created using BrainNet Viewer (https://www.nitrc.org/projects/bnv/).

Table 2
Regression analysis with group, anhedonia score and the interaction effect between group and anhedonia score.

Cluster size	Hemisphere	Brain Region	Brainnetome Altas	Peak MNI Coordinates			p value (FWE corrected)
				X	Y	Z	
Group Effect							
Right NAc core-like subdivision[a]							
205	Left	mid-anterior OFC	lateral area 11	−20	30	−16	0.005
221	Right	IPL	caudal area 40 (PFm)	58	−48	38	0.003
Left NAc core-like subdivision[a]							
149	Right	MFG	dorsal area 9/46	30	30	32	0.027
Anhedonia Effect							
Right NAc core-like subdivision[b]							
292	Right	Vermis	–	2	−68	−38	0.001
Interaction Effect Between Group and Anhedonia							
Right NAc shell-like subdivision[a]							
143	Left	sgACC/pgACC	subgenual area 32	−6	34	2	0.025
Right NAc core-like subdivision[a]							
132	Right	precuneus	area 31 (Lc1)	4	−58	18	<0.001

Note: [a] Each of functional connectivity maps of NAc subregions separately entered into the multiple regression model as the independent variable, and TEPS consummatory score, group, and group* TEPS consummatory as covariates of interest; [b] Each of functional connectivity maps of NAc subregion separately entered into the multiple regression model as the independent variable, and TEPS anticipatory score, group, and group* TEPS anticipatory as covariates of interest. Abbreviations: lateral OFG, lateral orbital gyrus; IPL, inferior parietal lobe; MFG, middle frontal gyrus; sgACC, subgenual anterior cingulate cortex; pgACC, pregenual anterior cingulate cortex; MDD, major depression disorder; HC, health control; TEPS, Temporal Experience of Pleasure Scale; PFm, parietal area F, part m, which belongs to temporo-parieto-occipital junction.

connectivity maps of NAc subregions as input separately, and TEPS consummatory score, group, and group* TEPS consummatory as covariates of interest, we found significant effects of the MDD group on the rsFC between the right NAc core-like subdivision and the left mid-anterior OFC (FWE corrected $p = 0.005$) and the right inferior parietal lobe (IPL) (FWE corrected $p = 0.003$) as well as between the left NAc core-like subdivision and the right middle frontal gyrus (MFG) (FWE corrected $p = 0.027$) (Table 2). Compared with the HC group, these

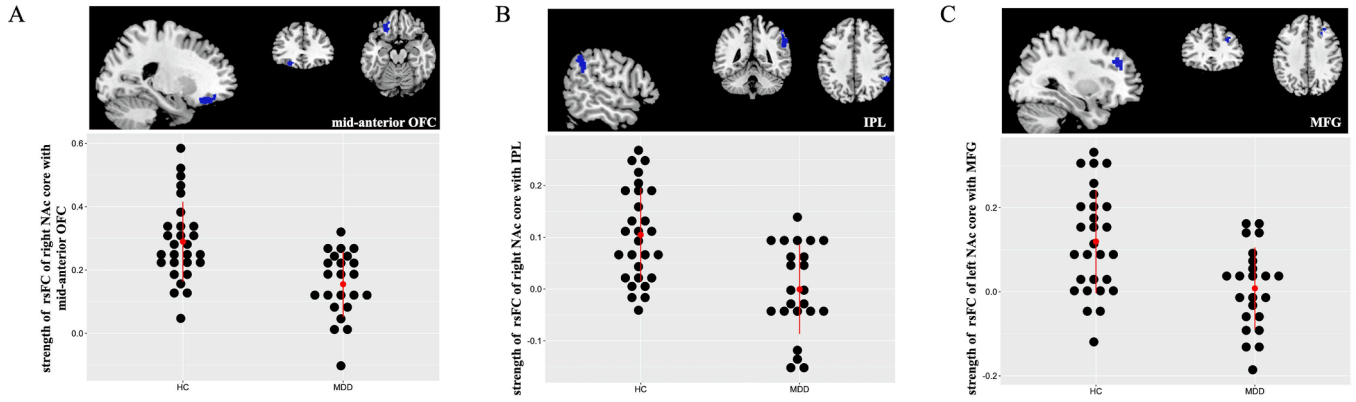

Fig. 3. Group effects on the resting-state functional connectivity of the NAc subregions. A-C shows the regions showing a significant group effect in the resting-state functional connectivity of the right NAc core-like subdivision with the TEPS consummatory score as one of the covariates. Compared with the HC group, the strength of all functional connectivity decreased in the MDD patients. Abbreviations: see Table 2.

rsFCs showed significantly decreased in the MDD patients (Fig. 3).

There were no significant effect of group and group*TEPS anticipatory on the rsFC of NAc subregions.

In addition, we found a significant interaction effect between the MDD group and the TEPS consummatory score on the rsFC between the right NAc shell-like subdivision and the left sgACC/pgACC (FWE corrected $p = 0.025$) (Table 2). According to the simple effect analysis, the strength of the rsFC between the right NAc shell-like subdivision and the left sgACC/pgACC was positively correlated with the TEPS consummatory score for the MDD patients ($\beta = 0.005$, $t = 2.17$, $p = 0.04$), but was negatively correlated for the HC group ($\beta = -0.006$, $t = -2.20$, $p = 0.03$) (Fig. 4A).

Further, we also found a significant interaction effect on the rsFC of the right NAc core-like subdivision with the precuneus (FWE $p < 0.001$) (Table 2). The simple effect analysis showed that the strength of this rsFC was negatively correlated with the TEPS consummatory score for the HC group ($\beta < 0.0001$, $t = -3.16$, $p = 0.003$), but was not correlated for the MDD patients ($\beta = 0.005$, $t = 1.8$, $p = 0.08$) (Fig. 4B).

Additionally, in the linear regression model analysis with the rsFC between the right NAc shell-like subdivision and the left sgACC/pgACC or with the rsFC between the right NAc core-like subdivision and the precuneus as the dependent variable, the VIF of TEPS consummatory score, MDD status and the interaction variables were 1.56, 1.31 and 1.17, respectively, suggesting that the variables had acceptable multicollinearity (Akinwande et al., 2015).

4. Discussion

The present study used rsfMRI to investigate the differences in the relationship between the functional connectivity of the NAc subregions and anhedonia among MDD patients and HC. Our results revealed significantly decreased connections between the right NAc core-like subdivision and the left mid-anterior OFC and the right IPL among MDD patients. In addition, there were also significantly decreased connections between the left NAc core-like subdivision with the right MFG among the MDD patients. Furthermore, the MDD patients differed from the HC in the correlates of the rsFC of NAc subregions with anhedonia. That is, both of the correlates of the functional connectivity of the right NAc core-like and shell-like subdivisions with anhedonia were modulated by depression. Taken together, these results suggest that the NAc subregions may play different roles in the neural basis of anhedonia in MDD patients and HC.

We found that the functional connectivity of the NAc core-like subdivision with the left mid-anterior OFC, right MFG (area 9/46d in Brainnetome Atlas (Fan et al., 2016)) and right IPL was decreased in the patients with MDD. The mid-anterior OFC, a core region in hedonic circuits (Berridge and Kringelbach, 2008), has been found to play a key role in subjective hedonic experience (Berridge and Kringelbach, 2015; Kringelbach et al., 2003) and explicit hedonic judgment (Zou et al., 2016). The MFG (area 9/46d), a part of the dorsal lateral prefrontal cortex (DLPFC) (Petrides and Pandya, 2012; Sanches et al., 2009), is associated with anhedonia and eudemonia well-being in previous studies (Heller et al., 2013). The IPL represents task-reward associations

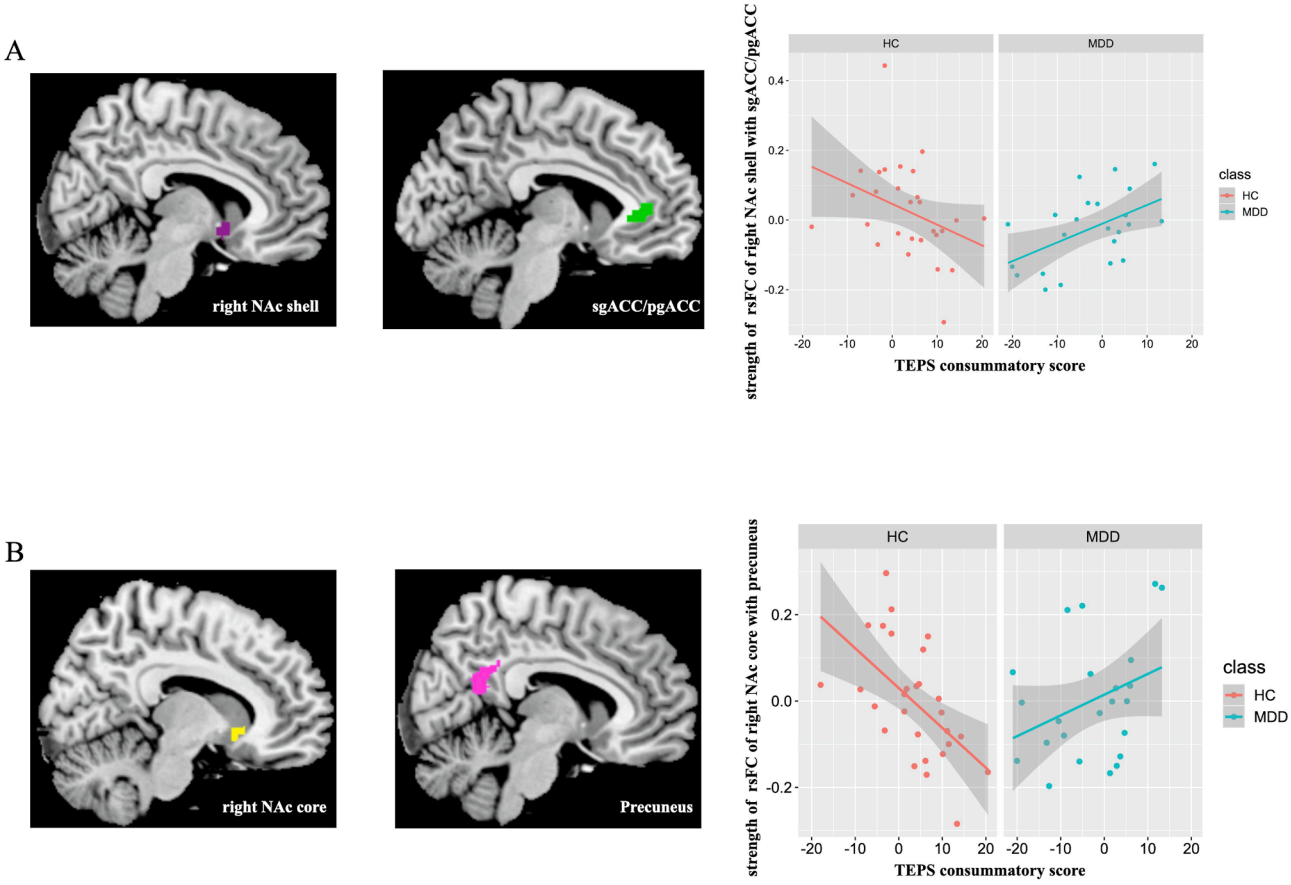

Fig. 4. The group by the anhedonia score interaction effects on the right NAc shell-like subdivision and core-like subdivision. The left figure in the Panel A showed the location of sgACC/pgACC, and the right figure used a scatter plot to show the correlation between the TEPS consummatory score and the connectivity strength in the sgACC/pgACC in the MDD patients and HC, respectively. The left figure in the Panel B shows the location of precuneus, and the right was a scatter plot to show the correlation between the TEPS consummatory score and the connectivity strength in the precuneus in the MDD patients and HC, respectively. Note: The TEPS consummatory score was adjusted after controlling gender, age, education and mean FD value.

(Wisniewski et al., 2015) and relates to a visual stimulus-coupled reward in decision-making (Guo et al., 2013). All of these findings suggest that the mid-anterior OFC, MFG (also called DLPFC), and IPL are involved in hedonic and reward processing. A recent rsFC study identified the medial OFC (very close to the mid-anterior part of the OFC in this study) as a nexus of hypoconnectivity to the other regions in MDD patients compared with the HC (Cheng et al., 2016). The activation of the dorsal and middle frontal regions were decreased in the MDD patients during both reward selection and anticipation (Smoski et al., 2009). Furthermore, a decreased functional connectivity between the NAc and the IPL was also reported in MDD patients (Gong et al., 2018). Based on the role of the mid-anterior OFC, MFG, and IPL in hedonic and reward processing and their decreased functional connectivity in previous studies of MDD, we speculate that the current finding of the decreased rsFC of the NAc core-like subdivision with these regions in MDD patients suggests a disrupted reward system in MDD with anhedonia. This disrupted reward system may lead to the dysfunction of motivation and subsequently decision-making, which is often observed in MDD patients (Rizvi et al., 2016).

More importantly, we found that the neural correlates of anhedonia were modulated by depression and the modulatory effect was regionally-dependent on the rsFCs of the NAc subregions. Specifically, we found a significant interaction effect between consummatory anhedonia and group on the rsFC between the right NAc shell-like subdivision and the left sgACC/pgACC as well as on the rsFC between the NAc core-like subdivision and the precuneus. A previous study found that the left ACC (including sgACC and pgACC) was associated with consummatory anhedonia in MDD patients (Zhang et al., 2016). In addition, both of the sgACC and pgACC is a part of the vMPFC (Dixon et al., 2017; Roberts and Clarke, 2019). The abnormal activations of the vMPFC were observed during the consummation phase among young people with depression symptoms (Rzepa et al., 2017). Furthermore, the interaction between the NAc and vMPFC has been shown to be pivotal for reward anticipation and receipt (Schreiter et al., 2016). Having a closer look on the interaction effect between consummatory anhedonia and group on this rsFC of the NAc subregion in the vMPFC, we found a positive correlation between this rsFC and consummatory anhedonia in the MDD patients, but an opposite pattern was found in the HC. The positive correlation found in the MDD patients suggests that higher anhedonia (lower TEPS score) is correlated with lower connectivity strength in MDD. This pattern is consistent with previous studies, in which the lower rsFCs of the NAc with the pgACC and the posterior vMPFC were associated with greater anhedonia in the MDD patients (Gabbay et al., 2013; Young et al., 2016). In addition, another study found that higher anhedonia in MDD patients was associated with a decreased functional connectivity between the DLPFC and the right NAc in response to reward cues following positive mood induction (Green et al., 2019). On the contrary, we found a negative correlation pattern in the HC, suggesting higher anhedonia (lower TEPS score) is correlated with higher rsFC of the NAc subregion. This is similar to previous studies, in which higher trait anhedonia was found to be correlated with the higher BOLD signal of the vMPFC during the processing of pleasant stimuli in the health individuals (Harvey et al., 2007; Keedwell et al., 2005). This implied that individuals who found it more difficult to feel happy in response to happy stimuli displayed a greater vMPFC response, although contradictory evidence also existed (Harvey et al., 2010; Keller et al., 2013; Wacker et al., 2009). It needs to be noted that these previous findings focused on local brain activity, whereas the current study extended the neural correlates of anhedonia in the HC by using the resting-state functional connectivity. Two explanations were proposed to account for the higher activity in the vMPFC in the anhedonic non-clinical individuals. One possibility owes to a PFC compensatory mechanism for an under-active striatal response to pleasant stimuli. Another is based on the corticolimbic inhibitory interactions (Harvey et al., 2007). Along this line, this higher functional coupling between the vMPFC and the NAc in the anhedonic non-clinical individuals may also reflect the PFC compensatory mechanism or the corticolimbic inhibitory interactions. Further studies need to be done to explore the potential mechanisms.

A small number of studies focus on the role of the precuneus in reward or hedonia. In a recent study, hedonic well-being was found to be negatively correlated with the functional connectivity of the precuneus and the MPFC (including vMPFC) in the HC. In addition, the balance of eudaimonic and hedonic well-being was positively correlated with the functional connectivity of the bilateral vMPFC as well as the bilateral precuneus (Luo et al., 2017). It is notable that both the vMPFC and the precuneus are core nodes in a default mode network (DMN). They belong to the anterior and posterior part of the DMN, respectively (Andrews-Hanna et al., 2010). The DMN is important to internally directed forms of cognition and individuals' perceived level of hedonia and eudaimonic well-being (Luo et al., 2017). The decreased connectivity of the DMN with the NAc is related to the reward deficits in patients with psychiatric disorders (Sharma et al., 2017). Although both the anterior and posterior parts of the DMN are related to spontaneous or self-generated cognition, the anterior and posterior DMN differ with respect to their specific functions (Mulders et al., 2015). The anterior DMN is more related to self-referential processing and emotion-regulation, while the posterior DMN related to both consciousness and memory processing. As to the rsFC with the NAc, the vMPFC has a positive connectivity with the NAc subregions, especially the shell-like subdivision, but the precuneus has a negative connectivity with the NAc subregions in healthy subjects (Xia et al., 2017). Thus, our findings provide additional support to the functional dissociation of the anterior and posterior DMN, which indicates that there might be a dissociable connectivity pattern of the NAc subregions with the DMN subnetworks related to anhedonia and that this pattern can be modulated by depression.

Further, we found that depression only modulates the neural correlates of consummatory anhedonia and not anticipatory anhedonia *per se*. Consummatory anhedonia is marked by a decreased enjoyment of currently experienced pleasant events (Li et al., 2015). The consummatory pleasure deficit is considered a main contributor to MDD in patients with anhedonia (Chow et al., 2018). Previous studies found that the MDD patients with lower consummatory pleasure corresponded to those that had blunted emotional reactivity to positive stimuli and showed less pleasure experience towards daily events (Bylsma et al., 2008, 2011). In addition, consummatory pleasure deficits caused decreased activation of the caudate (Zhang et al., 2013). Furthermore, we only found neural correlates of anhedonia in the cerebellum in both the MDD patients and the HC, which suggests that no rsFC between the NAc subregions and other regions, such as PFC, showed consistent correlation with anhedonia across the MDD patients and HC. These findings provide additional evidence that the MDD patients differ from the HC in the neural correlates of anhedonia.

The present study has some potential limitations. First, most of the MDD patients in the present study were medicated and the antidepressant drugs may influence the brain functions of these patients. Therefore, future studies with first episodic, drug naïve MDD patients are encouraged. Second, the study used self-reported questionnaires to measure anhedonia in the MDD patients. Studies with specific tasks that assess anhedonia or related psychological processes may be helpful to further enrich our understandings on the neural correlates of anhedonia in MDD. Third, the history of psychiatric conditions of HC was assessed by a self-report questionnaire. Future studies need to use the SCID to assess the HC to ensure that they do not have any known psychiatric conditions. Fourth, this study used a common GRE-EPI pulse sequence to obtain functional MRI images, which resulted in a relatively low spatial resolution of the images. Although we observed differential shell vs core connectivity across the participants using these images, future studies should use a high spatial resolution fMRI to improve location accuracy of the NAc shell and core, such as simultaneous multi-slice excitations with multiband radiofrequency pulses (Moeller et al., 2010). Finally, due to this is an exploratory study and the sample size was relatively

small, we did not conduct further multiple comparison corrections for the 8 separate multiple regression analyses, although we noticed that a couple of these findings in this study could survive Bonferroni correction (with 8 analyses, at $p < 0.006$), such as the rsFC of right NAc core-like subdivision. Future study with large sample is needed to validate the generalizability of these findings.

5. Conclusions

In summary, this study found decreased functional connectivity between the core-like subdivision of the NAc and the frontoparietal regions, especially the OFC, are involved in the hedonic experience among MDD patients. More importantly, we found that the neural basis of consummatory anhedonia is different between the MDD patients and HC subjects, which suggests that a dissociable connectivity pattern of the NAc subregions with the anterior and posterior DMN subnetworks may be involved in anhedonia. The modulation effect of depression on the relationship between anhedonia and the rsFCs of the NAc subregions suggests that the neural correlates of anhedonia may be not continuous and linear across participants. Combined these findings with the lower TEPS scores in the MDD patients, our current study suggests that ability to enjoy pleasure experience may be related with the functional coupling between the brain regions involved in the reward and reward-related emotion processing, however this relationship may be changed with the depression status. This nonlinear relationship between trait or behavior and brain activity across HC and patients with psychiatric disorders has been observed in previous studies (Van Snellenberg et al., 2016; Zhuo et al., 2020). Our findings extend our knowledge on the brain-behavior relationship and enrich our understanding of the neural basis of anhedonia in MDD.

CRediT authorship contribution statement

Rui Liu: Data curation, Formal analysis, Software, Writing - original draft. **Yun Wang:** Investigation, Writing - review & editing. **Xiongying Chen:** Formal analysis. **Zhifang Zhang:** Formal analysis. **Le Xiao:** Investigation, Resources. **Yuan Zhou:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contributors

Rui Liu analyzed imaging data and completed the manuscript. Yun Wang collected the original imaging data, and assisted with the paper revision. Xiongying Chen and Zhifang Zhang commented to the data analysis method. Le Xiao collected the original imaging data. Yuan Zhou designed this study and provided the significant comments to the manuscript. All authors approved the manuscript for submission.

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