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Short communication

Main text:1974 words; 1 Figure; 1Table; 20 references

## **Anhedonia reduction correlates with increased ventral caudate connectivity with superior frontal gyrus in depression**

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## **1. Introduction**

Anhedonia, a core depressive criterion marked by the reduced ability to feel pleasure in normally pleasurable activities, is thought to reflect a dysfunctional processing of reward on a neurobiological network level (Hoflich et al., 2019). Several studies have shown that the disruption of reward processing is associated with reduced functional connectivity (FC) in the frontostriatal projection in patients with major depressive disorder (MDD) (Furman et al., 2011; Gong et al., 2017). Longitudinal studies to identify potential biomarkers associated with a reduction in anhedonia are necessary for the development of novel treatment targets.

The ventral caudate, a key component of the ventral striatum, is associated with reward processing. Disruption of caudate activation was also associated with monetary gain and losses in patients with MDD (Admon et al., 2015; Pizzagalli et al., 2009). Using caudate-seeded resting state FC analysis, the ventral caudate has been shown to connect strongly with the orbitofrontal cortex and ventral medial prefrontal cortex (Huang et al., 2017; Jung et al., 2014). Structural studies have shown an inverse relationship between anhedonia and caudate volume in a healthy population (Harvey et al., 2007) and unmedicated MDD patients (Pizzagalli et al., 2009). We have previously shown that anhedonia correlated with diminished left ventral caudate and superior temporal gyrus BOLD activity to effort-based decision making in patients with first episode MDD (Yang et al., 2016). We also found that anhedonia correlated with reduced left ventral caudate connectivity with the superior frontal gyrus, the superior parietal lobule and the middle temporal gyrus, as well as increased superior temporal gyrus connectivity with the precuneus, the angular gyrus and the cuneus in first-episode patients (Yang et al., 2017). However, it is not clear whether the functional changes in these brain regions will be associated with improved anhedonia symptoms over time during the natural history of the disease.

The aim of the present study was to examine the relationship between resting state FC and 1-year outcome of first-episode drug-naïve MDD patients. Three bilateral seeds, the ventral caudate, the dorsal caudate and the superior temporal gyrus, were chosen to examine whether alterations in functional connectivity within these brain regions would be associated with a

reduction in anhedonia severity over time. Given that increased cortico-striatal functional connectivity was associated with MDD remission (Dichter et al., 2015), we hypothesized that reduced connectivity between the ventral caudate and prefrontal cortex at baseline would be ameliorated during the 1-year period. We further hypothesized that the FC increase would be correlated with anhedonia improvement in patients with MDD.

## **2. Method**

### **2.1 Participants**

Inclusion/exclusion criteria and fMRI results at baseline have been reported previously (Yang et al, 2017). In brief, seventy-six right-handed participants were recruited in baseline study. Forty patients were having their first episode of MDD without any medication treatment. Exclusion criteria were any other axis I disorders and poor cognition. For comparison, 36 healthy controls (HC) were matched for age, gender, IQ estimates. Healthy controls had no current or past personal history of any axis I disorders. Four MDD patients were excluded due to diagnosis change in the follow-up period: two developed manic bipolar disorder, one developed schizophrenia, and one developed anxiety with panic attacks. Twenty participants (10 MDD, 10 HC) were lost to follow-up because their telephone number changed, 17 participants (3 MDD, 14 HC) refused to join the second imaging scan. The final sample included 19 MDD patients (female 57.89%) and 16 HC (female 56.25%) from March 10, 2015, to August 24, 2016. All patients are right-handed. No difference was found in age, gender, IQ estimates and head motion (Table 1). The follow-up rate was 46.17% (35/76). The duration of time between scans was 1.14 (SD=0.16) years in the MDD group, and 1.22(SD=0.17) years in the HC group.

Eleven patients were found to be fully remitted and 8 were still depressed (non-remitted) according to the criteria of Frank et al. as a 17-item HAMD (HAMD) score of 7 or less (Frank et al., 1991). All patients were under anti-depressive treatment except that one patient was treated with cognitive therapy for 12 trials. Twelve patients received selective serotonin reuptake inhibitors (SSRIs) treatment, 3 patients were under noradrenergic and specific

serotonergic antidepressants (NaSSAs) treatment, 3 patients took serotonin-norepinephrine reuptake inhibitors (SNRIs). No patient had received electroconvulsive therapy (ECT). After 1 year, 8 patients stopped antidepressant treatment, and 11 patients were still taking antidepressants. The mean length of medication treatment was 8.09 (SD=5.93) months. All participants gave written informed consent. Participants were paid 50 RMB for each imaging session. The study was approved by the Institutional Review Board of the Central South University (2017089).

## 2.2 Measure

The Chinese versions of Beck Depression Inventory was used to measure the severity of depression (Wang et al., 1999). The Chinese versions of the 14-item Snaith-Hamilton Pleasure Scale (SHAPS) was used to assess the severity of state anhedonia (Liu et al., 2012), whereas the 20-item Temporal Experience of Pleasure Scale was used to measure the anticipatory (TEPS-ANT, 'wanting') and the consummatory (TEPS-CON, 'liking') component of pleasure experience (Chan et al., 2010), which marked by anticipate pleasure in the future for normally pleasurable activities or the reduced ability to feel pleasure in the present.

## 2.3 Functional connectivity analyses

Data acquisition and preprocessing have been reported previously using DPARSF programs (<http://www.restfmri.net>) (Yang et al., 2017). No participant with head motion (Frame-wise Displacement, FD) was greater than 0.2mm. To minimize nuisance confounds, the whole-brain signal, six motion parameters, cerebrospinal fluid (CSF) and white matter signals were regressed out. The following six seed regions of interest (ROI) were then selected: the bilateral ventral caudate (VC;  $\pm 10, 15, 0$ ), the bilateral dorsal caudate (DC;  $\pm 13, 15, 9$ ) and the bilateral superior temporal gyrus ( $\pm 45, -33, 12$ ) that demonstrated functional decoupling during an effort-based decision-making task evoking motivational anhedonia in first-episode patients (Yang et al., 2016). The radius of each seed was 4 mm. Briefly, the averaged time series were obtained from each seed region and functional connectivity maps were produced by computing Pearson's correlation coefficients between each seed and voxels of the whole brain. The correlation coefficient maps were converted into Z maps using Fisher's r-to-z transformation.

A repeated measure analysis of variance (ANOVA) for the functional connectivity maps within each seed region in SPM12 was specified to examine the relationship between baseline and follow-up variables, including a main effect of time (year 0 vs 1), a main effect of group (MDD patients vs HCs), and a group  $\times$  time interaction. In the Flexible Factorial model, one repeated measure variables (time), one between-groups variable (group) and one between-subjects variable (subject) were included. Age, gender, IQ, the length of medication and FD were entered as covariates. Significance was determined using an uncorrected voxel-level cluster-forming threshold of  $p < .001$  and a cluster-level FWE-corrected threshold of  $p < 0.05$  across the whole-brain ( $p < 0.05$ ). Mean z values for each group were extracted from surviving clusters within each ROIs and entered into an ANOVA in SPSS 22 to probe pairwise post hoc comparisons between groups at Bonferroni-corrected  $p < 0.05$  and interaction effects. To further elucidate the clinical meaning of the findings, Pearson's correlations were calculated between difference in Z values and symptoms improvement from baseline to follow-up in patients and healthy controls.

### **3.Results**

As shown in Table 1, the Group  $\times$  Time interactions were significant for depression severity and three types of anhedonia. Simple effects testing with Bonferroni-corrected comparisons suggested that, compared with baseline, MDD patients were decreased in depression severity, state anhedonia, anticipatory and consummatory anhedonia (all  $p < .001$ ) one-year later. However, no such significant findings were found in the HC group. There were not significant differences in age, gender, education, IQ and FD between groups.

An interaction effect of group and follow time was observed across the overall MDD and HC groups for connectivity between the left ventral caudate ROI and the left superior frontal gyrus ( $x=-12$ ,  $y=48$ ,  $z=36$ , cluster size=40, peak  $z=4.15$ , FWE corrected  $p=.014$ ). Repeated ANOVA revealed the significant interaction (Group $\times$ Time) for the extracted mean Z value for connectivity between the left ventral caudate and the left superior frontal gyrus between the MDD group and HCs ( $F_{(1,33)} = 8.02$ ,  $p=.008$ ,  $\eta^2=0.20$ , Figure1). Bonferroni-

corrected post hoc pairwise comparisons revealed a significant increase in the left ventral caudate connectivity with superior frontal gyrus from baseline ( $M=0.01$ ,  $SD=0.03$ ) to one-year later ( $M=0.16$ ,  $SD=0.03$ ) in the MDD patients ( $p=.002$ ; mean difference= $-0.15$ , 95% CI ( $-0.24$ ,  $-0.06$ )). In the baseline, the left ventral caudate connectivity with superior frontal gyrus in MDD was significantly reduced compared to that of HC ( $M=0.14$ ,  $SD=0.04$ ,  $p=.013$ ; mean difference= $-0.13$ , 95% CI ( $-0.22$ ,  $-0.03$ )). However, no group difference was found one year later. HC did not show any significant change between baseline and one-year later. No significant result was found for the resting state FC of dorsal caudate and superior temporal gyrus.

For the MDD group, SHAPS difference (follow-up minus baseline) correlated negatively with increased left ventral caudate connectivity ( $r=-0.50$ ,  $p=.031$ ) whereas TEPS-CON difference correlated positively with increased left ventral caudate connectivity ( $r=0.48$ ,  $p=.039$ ). In addition, TEPS-ANT difference, the length of medication and change in depression severity did not correlate with the left ventral caudate connectivity with superior frontal gyrus. For the HC group, SHAPS difference was not correlated with increased left ventral caudate connectivity ( $r=0.30$ ,  $p=.25$ ) whereas TEPS-CON difference correlated negatively with the left ventral caudate connectivity ( $r=-0.55$ ,  $p=.029$ ). Considering the small sample size, an uncorrected statistical significance level of  $p<0.05$  was used.

#### **4. Discussion**

Overall, 68% of patients had a recovery in the 1-year follow-up period. Compared with baseline, the MDD patients exhibited significant elevation in the left ventral caudate connectivity with the superior frontal gyrus after 1 year whereas there was no change in connectivity of the dorsal caudate or superior temporal gyrus. Moreover, the functional connectivity increases in the left ventral caudate were significantly associated with improvement in self-reported anhedonia severity during a 1-year period, but not with overall depressive severity, suggesting the left ventral caudate may be a potential biomarker for progression of anhedonia severity.

Previous studies have reported that recovery of function in brain regions could be related to reward processing. Specifically, greater activation in the left ventral striatum was associated with a decrease in anhedonia symptoms during a 6-month period (Eckstrand et al., 2019). Increased neural response in the ventral striatum during anticipation of monetary reward in unmedicated MDD patients was found after 6 weeks of antidepressant treatment. This increase in the ventral striatum was associated with a reduction in self-reported anhedonia (Stoy et al., 2012). In addition, an increase in fronto-striatal FC was also found to positively correlate with improvement in positive affect after 2 months of antidepressant treatment (Heller et al., 2013). A potential mechanism for the changes is that increased ventral caudate connectivity might be associated with an increased regulatory effect of prefrontal cortex over the ventral caudate leading to better emotional processing ability and motivated drive. In line with this, There is mounting evidence from reward task-based fMRI that reduced activity in the striatum is important in the etiology of depression. For example, reduced left caudate response to rewards has been found in MDD patients with anhedonia (Yang et al., 2016). Similarly, lower bilateral ventral striatum activation to anticipated monetary reward was associated with the onset of major depressive disorder during a 2-year period, and the left reduced ventral striatum activity was specific to anhedonia (Stringaris et al., 2015). This provides further evidence that the left ventral striatum may be a particularly salient neural target for improving anhedonia in MDD, which supports the importance of examining the laterality of potential biomarkers associated with future clinical and psychosocial outcome measures in MDD.

In addition, it should be noted that the ventral and dorsal caudate subdivisions are relatively segregated. The ventral caudate together with the dorsolateral prefrontal cortex have been postulated to support reward-related processing and emotion, while the dorsal caudate, in association with dorsal lateral prefrontal regions, is involved in cognitive control (Di Martino et al., 2008). In the present study, MDD patients exhibited increased connectivity in the ventral caudate and no alterations at the dorsal caudate, suggesting MDD patients exhibit improvement in the reward processing network, but not in the network for cognitive control, associated with reduction of anhedonia severity. ,



The present findings should be regarded as preliminary given that the sample size prevented us from comparing individuals who reached remission vs. those who did not. However, an exploration analysis found that remitted subgroup showed an increased left ventral caudate connectivity with the left superior frontal gyrus ( $x = -21, y = 42, z = 39$ , cluster size = 32, peak  $z = 3.8, p = .003$ ) compared with non-remitted patients, suggesting that a failure to increase the left ventral caudate connectivity may be related to a poor clinical outcome. Further studies with larger sample sizes are needed to elucidate this important topic. Another potential limitation was that the follow-up sample size was reduced compared to the original set of patients and healthy participants, mainly owing to loss of contact or moving to other cities for work. This dropout, although regrettable, did not affect our results. Indeed, an exploratory analysis between drop-out and follow-up patients at baseline did not show any significant difference in functional connectivity, age, gender, or depression and anhedonia severity. Finally, it is regrettable that all patients but one were treated with anti-depressive treatment, as the effect of medication on the connectivity of ventral caudate is of experimental interest. It would also be important to stratify by gender in analyses, as there are twice as many females experiencing major depression as males (Salk et al., 2017).

In summary, the results of this study observed an increase in the left ventral caudate connectivity with bilateral superior frontal gyrus after 1 year in MDD patients, which was associated with anhedonia reduction.

## Figure Legends

**Fig.1.** Increased functional connectivity between the left ventral caudate seed region and the superior frontal gyrus in the MDD group over time when compared with the HC group. Bar plots showing significant interaction in average Z-transformed correlation coefficients for the superior frontal gyrus. The error bar represents standard error. All images are displayed at FWE correction  $p < .05$ . Scatterplots between anhedonia and increase the left ventral caudate connectivity in each group. Higher scores in the Snaith-Hamilton Pleasure Scale (SHAPS) indicate higher levels of state anhedonia whereas lower scores the Temporal Experience of Pleasure Scale (TEPS) indicate higher levels of anhedonia.

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