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The functional connectivity between nucleus accumbens and the ventromedial prefrontal cortex as an endophenotype for bipolar disorder

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Running title: NAcc/vmPFC connectivity in bipolar disorder

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Abstract

Background: Alterations in functional connectivity between the nucleus accumbens (NAcc) and frontal cortices have been previously associated with the presence of psychiatric syndromes, among them bipolar disorder. Whether these alterations are a consequence or a risk factor for mental disorders remains unresolved.

Methods: This study included 35 bipolar participants, 30 of their resilient siblings, and 23 healthy controls to probe functional connectivity at rest between NAcc and the rest of the brain in a cross-sectional design. BOLD time series at rest from NAcc were used as seed-region in a voxel-wise correlational analysis. The strength of the correlations found were compared across groups after Fisher’s Z transformation.

Results: Our results showed increased functional connectivity between NAcc and a ventromedial prefrontal cortex (vmPFC) - comprising mainly the subgenual anterior cingulate - in patients compared to controls. Participants at increased genetic risk but yet resilient – i.e. unaffected siblings - showed functional connectivity values midway between the former two groups.

Conclusions: Our results are indicative of the potential for the connectivity between NAcc and the vmPFC to represent an endophenotype for bipolar disorder.
Introduction

Psychiatric disorders have a profound personal impact on sufferers and their families, also carrying an extraordinary societal burden. Despite increasing research efforts into the field, little advance has been made with regard to our mechanistic understanding of psychiatric disorders, limiting our ability to develop new efficient interventions. Recent neuroimaging research has placed the focus on investigating the brain's functional networks, under the assumption that psychopathology arises from alterations in connectivity/wiring of the brain.

From a functional MRI (fMRI) perspective, recently accumulated evidence suggests the presence of altered brain connectivity – i.e. co-activation of different brain structures required to work together to efficiently produce a complex response - in most severe psychiatric disorders (e.g. bipolar disorder (BD)), and amongst those networks the so called ‘reward network’.

The reward network has been described as a cortico-basal ganglia circuit, in which the ventral striatum – mainly the nucleus accumbens (NAcc) in humans – occupies a central role; despite including a large number of subcortical and cortical regions (see for a comprehensive description of this network). This network underpins reward seeking and hedonic responses to positive stimuli, which are basic to animal and human behavior. Within this network, the NAcc interaction with the ventromedial prefrontal cortex (vmPFC) has shown to be pivotal in regulating responses to reward and emotional symptoms in psychiatric disorders. For example, previous research has stressed the relevance of abnormal NAcc activation in bipolar disorder (BD) and of its interaction with vmPFC during reward anticipation and receipt.

The present study aims to examine the existence of NAcc functional connectivity alterations in BD during the absence of acute symptoms. We hypothesize that patients with BD recruited during euthymia will present alterations in NAcc functional connectivity when compared with healthy low risk participants (HC). We expect these potential alterations to include parts of the vmPFC. The fact that our participants will be euthymic at the time of scanning will indicate that any alterations detected would represent a trait of the disorder rather than a reflection of a
psychopathological state. We are also interested in examining whether any alterations detected will extend into an at risk but yet resilient sample of participants – i.e. unaffected siblings (SIB) of BD patients aged above the most frequent age of onset for the disorder. Under the assumption of functional connectivity alterations representing an endophenotype of BD, we hypothesize SIB participants to sit in between BD and HC in terms of the strength of any connectivity alterations detected. Due to existing discrepancies with regard to the potential direction of this effects, we do not make any a-priori assumptions as to whether functional connectivity will appear increased or decreased in BD and SIB relative to HC.

Methods and Materials

Participants and materials

A total of 100 participants were recruited for this study (43 BD, 34 SIB and 23 HC). Participants with a previous diagnosis of BD were recruited through the National Centre for Mental Health (NCMH), after confirmation of their diagnosis by a trained clinician (XC) using the Mini International Neuropsychiatric Interview (MINI). The MINI was also used in non-affected siblings and healthy controls to ascertain for potential psychopathology. Non-affected siblings were contacted through recruited BD participants, and only one sibling per family was included. Healthy controls were recruited from the community via advertisement. General inclusion/exclusion criteria for all groups included: a) age 35-60, b) no personal history of psychotic or borderline personality disorder, c) no recent history – within the past year - of abuse of or dependence on alcohol or other substances, d) conforming to Cardiff University Brain Research Imaging Centre’s standard MRI safety protocols. Specific criteria for BD participants included: a) positive diagnosis of BD type I or type II, b) mood stability, defined as absence of major mood episodes and no changes in medication for at least one month prior to scanning, c) current euthymia, defined as current scores below 10 in both the Hamilton Depression (HD) and Young Mania (YM) scales. In the case of SIB participants, an added criterion was: a) no personal history of any mood or psychotic episode; and for HC participants:
a) no personal history of any mental disorder, b) no family history in first-degree relatives of any mood or psychotic disorders.

Other than the clinical instruments mentioned above, participants also completed the National Adult Reading Test (NART)\textsuperscript{22} to estimate premorbid IQ.

Three participants decided to withdraw from the MR scan, 2 no longer met inclusion/exclusion criteria on the day of the scan, and 7 were excluded due to failing data quality assurance (see Data analysis section). Therefore, the final sample included 35 BD, 30 SIB and 23 HC.

All participants gave written informed consent after receiving a complete description of the study and were paid £20 for participating. The study was approved by the local NHS Research Ethics Committee.

Imaging protocol

Resting state fMRI data were acquired with a gradient-recalled echo echo-planar imaging sequence (TR=2.5s; TE=35ms; FA=90°; FOV=211mm; 3mm\textsuperscript{2} in-plane resolution, ASSET acceleration factor=2) using a 3T GE HDx MRI scanner equipped with an eight-channel receiver head coil. The scan duration was 7.5 minutes, during which participants were instructed to lie still and keep their eyes closed, and foam cushions were used inside the head coil to minimise the degree of motion. Whole brain coverage was achieved with 44 interleaved slices (3mm thickness, 0.3mm gap). A total of 180 volumes were acquired, plus 4 dummy volumes to allow the longitudinal magnetisation to reach a steady state. In order to register resting state scans to standard space, a 3D FSPGR image was also acquired (TR=7.9; TE=3ms; TI=450ms; Flip Angle=20°; 1mm\textsuperscript{3} isotropic resolution).

Data analysis

Preprocessing
Data were first preprocessed and registered to a standard space using a pipeline constructed from the AFNI (http://afni.nimh.nih.gov/afni) and FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki) software packages. The preprocessing pipeline was designed to mitigate the effect of subject motion and physiological noise as far as possible, and consisted of the following steps: 1) de-spiking (3dDespike, AFNI); 2) motion correction (3dvolreg, AFNI) by registering all volumes to the first one; 3) nuisance regression (3dREMLfit, AFNI) with pre-whitening to remove cardiac and respiratory related noise, and residual motion related variance. Only the six estimated motion parameters, and not their temporal derivatives, were used to model residual motion variance, in order to do so parsimoniously, and thus limit the potential for removing variance of interest; 4) slice time correction (3dTshift, AFNI); 5) non-linear registration to 2mm MNI brain (FLIRT & FNIRT, FSL); 6) ANATICOR, bandpass filtering (0.01-0.8 Hz) and motion scrubbing performed in a single step (3dTproject, AFNI). ANATICOR regressors were derived from the lateral ventricles and a global white matter mask (FAST, FSL), as well as voxel-wise local white matter regressors to minimise sensitivity to motion. Volumes considerably corrupted by motion (and “scrubbed”) were defined as those with a frame-wise displacement (Euclidean norm) in excess of 0.25mm, and subjects with greater than 20% of volumes corrupted were excluded from further analysis. This threshold ensured that all subjects included had the equivalent of at least 6 minutes worth of resting fMRI data (Supplementary Figure S1 presents a post-hoc comprehensive analysis of movement, showing this not to differ across groups and is not a confounding factor for our main results).

Seed-based functional connectivity analysis

For each subject a NAcc seed time-series was derived from the bilateral nucleus accumbens probability mask included in the Harvard-Oxford subcortical atlas. From this NAcc mask a seed time-series was created by taking a probability weighted mean, ensuring that the contribution of individual voxel time-series was determined by their probability of being part of this NAcc based mask. For each subject the correlation between each voxel in the brain and the seed time-course
was calculated (3dTcorr1D, AFNI) and the resulting statistical parameter maps were spatially
smoothed by 8mm (FWHM) (3dmerge, AFNI) and Fisher’s Z transformed.

The NAcc functional connectivity network (Figure 1) was derived from all participants using
a one-sample t-test (3dttest++, AFNI). Voxel-wise differences between groups were tested
for using two-sample t-test (‘-Clustsim’ option in 3dttest++, AFNI). To account for multiple
tests, a model-free nonparametric approach was used (3dttest++, AFNI). This
permutation approach does not use a mathematical model for the spatial autocorrelation
function, and is the most robust method for keeping false-positive rates at the nominal
level for simple statistical models\textsuperscript{29}. Voxels included in the comparisons were confined to a
mask derived from the mean EPI image across all subjects - thus, excluding areas of substantial
signal dropout - discounting voxels from the lateral ventricles and white matter - eroded masks
taken from Harvard-Oxford atlas.

Post-hoc tests at the ROI level were performed to examine group differences in SIB v HC and
the BD v SIB in the vmPFC ROI that was identified in the voxel-wise BD v HC comparison. The
mean z-transformed correlation coefficient for the significant cluster was calculated for each
participant and compared between SIB v HC by means of Welch’s t-test and between SIB v BD
by means of paired t-test.

Results

Group characterization

Groups did not differ in age ($F(2,87)=0.85, p>.1$), gender distribution ($X^2(2, N=88)=0.06, p>.1$), performance in the NART ($F(2,76)=0.59, p>.1$) or weekly intake of alcohol units ($F(2,81)=1.12, p>.1$). As expected, though, groups differed in clinical symptoms, with BD participants
showing higher scores in the Young Mania Scale ($F(2,85)=13.43, p<.001$) and the Hamilton
Depression Inventory ($F(2,85)=18.47, p<.001$) than HC and SIB; albeit still indicative of low
presence of mood symptoms in accordance with their euthymic state (Table 1).
On average, BD participants in our sample (16 BD type I and 19 BD type II) experienced their first significant mood episode at age 18, but received a diagnosis of BD 12 years later on average. This could be partly explained by the fact that over 90% of them experienced low mood as first episode and were initially treated for depression. Six (17%) BD participants presented current comorbid anxiety disorders - agoraphobia being the most prevalent - but that figure rose to over a third of the sample (37%) when considering a lifetime prevalence. Due to the strict inclusion criteria, no other diagnoses were present in this sample. At the time of scanning, only 4 BD participants were free of psychotropic medication, over a third were taking antidepressants (n=14) and/or antipsychotics (n=13), and over half were on mood stabilizers (n=21). Half of the BD group (n=17) was prescribed a combination of at least two of the above classes of drugs. Only 2 SIB participants presented with mental health history, referring past history of generalized anxiety disorder (n=1) and health anxiety (n=1). Following our inclusion criteria, HC had no history of any psychiatric disorder; and neither HC or SIB were under any psychotropic medication at the time of this study.

**BOLD in the VS correlates with vmPFC in the overall sample**

In order to capture the whole of the NAcc connectivity network, we ran a voxel-wise correlation analysis using the BOLD time series in the NAcc as reference. Several brain areas were shown to be positively associated with the NAcc BOLD time course across the whole sample (Figure 1). These included subcortical structures bilaterally such as the caudate, amygdala, hippocampus, parahippocampal gyri, ventral thalamus and anterior putamen; and cortical areas such as the vmPFC, ventro-lateral prefrontal cortex, anterior cingulate, superior frontal gyrus, middle temporal gyrus, lingual gyrus and postcentral gyrus. No negative correlations survived correction for multiple comparisons.
BD and HC participants differ in the connectivity between VS and vmPFC

Based on the above whole brain correlation map, the voxel-wise comparison BP v HC participants resulted in a significant cluster in the vmPFC (center of mass at MNI x=-2, y=36, z=-10, 334 voxels, cluster-extent corrected p<.05), predominantly left lateralized (Figure 2A). This indicated increased positive association between BOLD time course in the NAcc and the vmPFC in BD compared to HC participants, but with this correlation within those two groups being significantly non-zero (p< 0.001). In light of recent research showing antipsychotic medication affecting resting state cortico-striatal connectivity, we compared the z-transformed NAcc-vmPFC correlation between patients under this class of medication and those not under antipsychotics, resulting in no significant effects (t(33)=0.97, p>.1); there was also no significant association – albeit a trend – between chlorpromazine equivalents of antipsychotic dosage and NAcc-vmPFC correlation within the BD group (r(n=35)= .30, p=.08). Lithium dosage (r(n=9)= .38, p>.1) or presence of mood-stabilizers – i.e. Lithium or antiepileptics – (t(33)=0.06, p>.1) did not significantly predict either the NAcc-vmPFC correlation.

Due to its proximity to the frontal sinuses the vmPFC is an area of the brain that is susceptible to signal dropout during EPI acquisitions. By restricting our analysis to a mask derived from the EPI images themselves (Figure 3A), we ensured that only voxels with sufficient signal were included. Figure 3B includes a histogram of the signal intensity from the group mean EPI data, showing that the 5-95 percentile range of voxels in the vmPFC cluster fall comfortably in the robust range of voxels indicating that signal dropout did not significantly degrade voxels in the vmPFC cluster.

SIB show lower VS-vmPFC than BD, but higher than HC
Post-hoc ROI analyses using the vmPFC mask from the above analysis to compare NAcc-vmPFC connectivity between SIB v HC and SIB v BD resulted in a significant group difference for both the former (t(49.93)= 3.09, p<0.005) and the latter comparisons (t-paired(23)= 2.21, p<0.05) (Figure 2B), with SIB showing an average correlation midway between the BD and the HC average correlations. In order to validate these results, we performed exploratory voxel-wise group comparisons (uncorrected p< .01) using SIB as the reference group. For SIB>HC a significant cluster emerged in the vmPFC with a center of mass at MNI x=-2,y=32,z=-10, containing 95 voxels of which 94 overlapped with the BD>HC cluster (Figure 2C). No clusters emerged in the vmPFC when comparing SIB and BD groups.

NAcc-vmPFC connectivity association with residual symptoms

The strength of the NAcc-vmPFC connectivity – i.e. z-transform correlation index – did not appear to be associated with the presence of residual symptoms of depression (Hamilton Depression score, r=-0.02, p>.1) or mania (Young Mania score, r= -0.18, p> .1) in our BD sample. Despite the lack of association, we added these scores – i.e. HD and YM - as covariates in our group comparisons to ascertain for any potential confounding effects. As expected, results remained the same as previously reported.

Discussion

The main aim of this study was to investigate potential alterations in the functional connectivity between the NAcc and the vmPFC in BD, and to examine whether similar alterations could be found in unaffected siblings of BD patients. Our results show these two brain regions to be positively associated within all groups, but differing in intensity across BD patients, their unaffected siblings and unaffected-unrelated HC participants, suggesting this biomarker may behave as an endophenotype for this disorder.

Our whole brain correlational analysis using the NAcc as seed region showed an extensive associative network that largely overlapped with previous published research\textsuperscript{31-33}. Importantly,
a whole brain comparison between BD and HC showed these two groups only differed in the
intensity of the association between NAcc and vmPFC – the latter mainly consisting of the left
pregenual anterior cingulate and the medial orbitofrontal cortex - with BD participants
presenting increased connectivity compared to HC. Ventral frontostriatal hyperconnectivity had
been previously reported in patients with/samples at risk for psychosis; and suggested to be
indicative of an excessive motivational drive that could give rise to psychotic experiences34.
However, excessive metabolic activity within and connectivity from this cortical area has also
been associated with depression35, and has been successfully used as a deep brain stimulation
target for treatment resistant depression36-37 and bipolar disorder38. Recent animal research
shows that activation of vmPFC induces inhibition of midbrain dopaminergic interactions with
the ventral striatum causing suppression of reward seeking behavior and therefore increased
depressive-like symptoms in rats12. Our results, though, suggest that abnormal connectivity
between vmPFC and NAcc in humans could represent a trait marker of mental disorder rather
than merely indicating the presence of depressive symptoms; as firstly our BD participants
where scanned during euthymia, and secondly the strength of this connectivity did not appear to
correlate with the presence of residual depressive or manic symptoms in our BD group.

Importantly, differences in the connectivity between the NAcc and the vmPFC cluster were
also found in non-affected siblings of our BD participants when compared to HC. It is worth
noting that our SIB sample represents a resilient group of genetically high-risk participants. BD
is highly heritable and as such first-degree relatives of patients carry an excess risk of the
disorder39. However, our SIB group was recruited solely in absence of any personal history of
mood disorders and psychosis and an age >35, indicating lower probability of developing BD or
psychosis in the future40. As such and considering also that consequently none of our SIB
participants were taking psychotropic medication, alterations in the connectivity between these
two brain areas can be considered a premorbid risk marker for BD, and a potential
endophenotype41 for the disorder.
Our study carries some limitations that require noting. As with most research including chronic patients, a potential confounding effect of medication is present. However, a recent review suggests that the effects of medication impact less on brain function than originally thought, and where it is affected this could mainly be in the form of type II errors due to normalization\(^{42}\). Furthermore, any medication effect would only affect the results from BD participants, and we have shown antipsychotics not to be associated with our main finding in this group. Moreover, the fact that we replicate the same finding—albeit attenuated—in non-medicated unaffected siblings, makes us believe that our results are not a consequence of medication status. Also, due to the modest sample size and in order to avoid the need for more stringent corrections for multiple comparisons, we could not further exploit the data in order to investigate, for example, potential compensatory mechanisms present in SIB that could explain resilience, or potential BD subtype differences with regards of NAcc-vmPFC connectivity. Future studies designed to answer those questions are warranted. Finally, the lack of any behavioral output related to reward seeking or hedonic reaction to reward in our study, precludes the possibility to validate the hypothesis that the altered connectivity found in this study relates to reward processing, although previous preclinical\(^{43}\) and clinical\(^{44}\) research would suggest that it is.

Summarizing, our results show an increased connectivity during rest between NAcc and vmPFC in euthymic BD participants compared to HC. Non-affected siblings of participating BD patients also showed increased connectivity in between these brain areas when compared to HC, albeit attenuated in comparison with their affected siblings. Therefore, we propose that this connectivity alteration represents a premorbid biomarker for BD with high potential to represent an endophenotype for this disorder associated with reward function. Future similar research in unipolar depression, schizophrenia or addiction, for which alterations in reward function have been described, should determine whether this biomarker is common to other mental disorders.
Acknowledgements

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Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.
References


Figure legends

Figure 1. Ventral Striatum brain network obtained from the whole sample. Warm colored areas showed positive correlation (corrected p<.05) with the average BOLD time course in the nucleus accumbens (yellow) obtained from the Harvard-Oxford subcortical atlas. No negative correlation survived correction for multiple comparisons. Color indicates size of the association (Fisher z-transformed correlation coefficient) according to the provided scale.

Figure 2. A: Cluster in the ventromedial prefrontal cortex showing increased association with the average BOLD time course in the ventral striatum in BD compared to HC (voxel-wise whole brain comparison). The color scale indicates the size of the difference (z-transform) between BD and HC. B: Intensity of the association between the average BOLD time course from the ventral striatum seed region and the ventromedial prefrontal cortex cluster obtained from the voxel-wise BD v HC comparison, for each experimental group. P values correspond to the Welch’s t-tests of the z-transformed Pearson correlation between SIB and each of the other two groups. C: Overlap between the cluster in figure 2.A and the equivalent cluster obtained in the voxel-wise exploratory (uncorrected p<.01) comparison between SIB and HC.

Figure 3. A: Column 1 shows the mean EPI image from a representative participant, column 2 shows the group mean EPI image, and column 3 shows the analysis mask. In each case the vmPFC cluster mask is overlaid. B: A histogram of voxel intensity values from the mean EPI image across all participants, with the 5,25,50,75, and 95 percentiles marked. Also marked is the median signal intensity from the vmPFC and the 5-95 percentile range is shown.
Tables

Table 1. Demographics and clinical symptoms – mean (standard deviation) - for participants included in the connectivity analyses

<table>
<thead>
<tr>
<th></th>
<th>HC (n=23)</th>
<th>BD (n=35)</th>
<th>SIB (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male n (%)</td>
<td>9 (39%)</td>
<td>13 (37%)</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>Age</td>
<td>44.00 (4.48)</td>
<td>44.71 (5.51)</td>
<td>46.03 (6.94)</td>
</tr>
<tr>
<td>NART</td>
<td>38.11 (4.47)</td>
<td>36.12 (6.89)</td>
<td>36.65 (6.12)</td>
</tr>
<tr>
<td>OH</td>
<td>7.02 (8.36)</td>
<td>12.79 (16.67)</td>
<td>11.96 (14.27)</td>
</tr>
<tr>
<td>YM</td>
<td>0.26 (0.61)</td>
<td>3.31 (3.87)</td>
<td>0.66 (0.84)*</td>
</tr>
<tr>
<td>HD</td>
<td>0.35 (0.88)</td>
<td>3.97 (3.78)</td>
<td>0.90 (1.12)*</td>
</tr>
</tbody>
</table>

*BD>HC, SIB

HC: healthy controls; BD: bipolar disorder SIB: non-affected siblings from bipolar disorder patients;

NART: National Adult Reading Test, the number of correct answers is reported; OH: alcohol consumption in weekly units; YM: Young Mania Scale; HD: Hamilton Depression Scale. **NART score was missing for 11 participants (due to time constrains or English not being their first language)** OH weekly intake data was missing for 6 participants, and YM and HD for 2 participants.
Figures showing brain scans at different z values:

- z = -54 mm
- z = -48 mm
- z = -42 mm
- z = -36 mm
- z = -30 mm
- z = -24 mm
- z = -18 mm
- z = -12 mm
- z = -6 mm
- z = 0 mm
- z = 6 mm
- z = 12 mm
- z = 18 mm
- z = 24 mm
- z = 30 mm
- z = 36 mm
- z = 42 mm
- z = 48 mm
- z = 54 mm
- z = 60 mm

Color bar indicating z(r) values from -0.3 to 0.3.
A: BP > HC

\[ x = -2 \text{ mm} \quad y = 36 \text{ mm} \quad z = -10 \text{ mm} \]

B: Correlation between NAcc and vmPFC

\[ \Delta z(r) \]

\[ 0.15 \quad 0.10 \quad 0.05 \quad 0.00 \]

\[ p = 0.037 \]

\[ p = 0.003 \]

C: (BP > HC) \cap (SIB > HC)

\[ x = -2 \text{ mm} \quad y = 36 \text{ mm} \quad z = -10 \text{ mm} \]
Image A shows Single subject EPI, Group mean EPI, and Analysis mask in axial, sagittal, and coronal views. The right side of the image displays a signal intensity histogram for group mean EPI, with a vmPFC cluster mask showing the 5-95 percentile range.
The Functional Connectivity Between Nucleus Accumbens and the Ventromedial Prefrontal Cortex as an Endophenotype for Bipolar Disorder

Supplemental Information

Supplementary Figure S1. A) Distribution of the number of volumes censored for each group; in all cases the median was low and for each group the majority of participants had no censored volumes. B) Participant’s mean FD values across groups, for which there were no significant differences. C) Scatter plot of mean FD plotted against the NAcc-vmPFC correlation. It can be concluded that participant’s motion did not contribute to the NAcc-vmPFC association.