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### Wired for pain, shaped by the mind

*Interactions between pain and psychopathology in pediatric and adult patient populations*

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# CHAPTER 6

NEUROLOGICAL AND BEHAVIORAL MARKERS OF NEGATIVE  
SYMPTOM SEVERITY IN PATIENTS WITH PSYCHOSIS

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# NEURAL AND BEHAVIORAL MARKERS OF NEGATIVE SYMPTOMS AND COGNITIVE IMPAIRMENT IN PATIENTS WITH PSYCHOSIS

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## **Abstract**

*Background and Hypothesis:* Negative symptoms impair functioning in patients with psychotic illnesses (i.e., schizophrenia spectrum disorders (SZ) and bipolar I disorder with psychotic features (BD)). Disruptions in reward-motivation neurocircuitry is hypothesized to underpin negative symptoms, and other core features of psychosis (i.e., cognitive impairment).

*Study Design:* In patients with psychosis (SZ=20, BD=24) and healthy controls (HC=27), we used neuroimaging to define gray matter morphological properties, resting-state functional connectivity, and white matter microstructure. We examined negative symptom severity with the Clinical Assessment Interview for Negative Symptoms (CAINS)), and reward-related motivation with the Effort Expenditure for Rewards Task (EEfRT)). The MATRICS Cognitive Consensus Battery (MCCB) evaluated cognitive performance.

*Study Results:* Reduced nucleus accumbens volumes and functional connectivity between the nucleus accumbens and parietal cortices were associated to higher CAINS Motivation and Pleasure sub-scores. Smaller nucleus accumbens volumes correlated with lower effort expenditure for high reward probability during the EEfRT. The fornix showed reduced fractional anisotropy in SZ and BD cohorts. Negative associations were observed between CAINS Motivation and Pleasure sub-scores and MCCB verbal learning and composite scores. In patients with SZ and BD, gray matter volume in cerebellar lobule VI corresponded with the extent of cognitive impairment but not negative symptoms.

*Conclusions:* Nucleus accumbens-based properties and reward-motivation deficits may serve as transdiagnostic markers of negative symptoms, while cerebellar lobule VI properties may inform cognitive impairment in patients with SZ and BD. These findings contribute to the neural and behavioral underpinnings of negative symptoms and cognitive impairment in psychotic illnesses.

**Key words:** CAINS, Cognition, Nucleus Accumbens, Cerebellum, Bipolar Disorder, Schizophrenia

## Introduction

Negative symptoms<sup>1</sup> are a significant source of disability for individuals with schizophrenia spectrum disorders (SZ)<sup>2-5</sup> or bipolar I disorder with psychotic features (BD)<sup>6-8</sup>. There is current consensus that negative symptoms span five domains, which include anhedonia, asociality, avolition, blunted affect, and alogia<sup>1</sup>. More broadly, negative symptoms have also been classified into impairments as either motivation or pleasure and emotional expression, with each entity arguably underpinned by distinct neurobiological mechanisms<sup>9, 10</sup>. For many patients, negative symptoms manifest early in illness, sometimes even emerging prior to the development of florid psychosis<sup>11-14</sup>. While negative symptoms, along with cognitive impairment, are the symptom domains most predictive of poor functional outcomes<sup>15, 16</sup>, they respond less well to treatment with antipsychotic medications than positive psychotic symptoms such as hallucinations and delusions<sup>17, 18</sup>. Hence, improving negative symptoms and cognitive impairment remains an unmet clinical need<sup>18, 19</sup>.

Negative symptoms can be difficult to measure, and second generation clinical instruments such as the Clinical Assessment Interview for Negative Symptoms (CAINS) have aimed to better define anhedonia and expressive impairments in patients with psychosis, while adding granularity in terms of probing anticipatory vs. consummatory anhedonia<sup>1, 20</sup>. While the CAINS and other measures are valuable for quantifying the negative symptom severity in a variety of settings, for example, in clinical trials, natural history studies, or routine clinical monitoring, these tools are often limited by patient and administrator bias and recall, their subjective nature, and their inability to provide biobehavioral insights into causes of negative symptoms in patients with psychosis<sup>21</sup>. Neuroimaging approaches have been pivotal in objectively interrogating neural correlates of negative symptoms and cognitive impairment in patients with psychosis. Previous neuroimaging studies have identified a network of central nervous system (CNS) structures including but not limited to the ventral and dorsal striatum, frontal cortices, amygdala,

hippocampus as well as cerebellar subdivisions with many of these CNS regions are involved in emotional dysregulation, anticipation of rewarding and aversive events, and positive and negative valence encoding<sup>4, 22-25</sup>.

The objective of the current prospective investigation was to utilize a dimensional approach<sup>26</sup> and define brain-behavior underpinnings of negative symptoms in adults with SZ or BD. In the same cohort of patients, we further investigated whether there are shared neural aberrancies (functional and structural) between negative symptoms and related core features of psychosis (i.e., cognitive impairment) given their overlapping pathophysiological mechanisms as well as neurocircuitry<sup>22, 27</sup>. Reward-motivational deficits and cognitive impairments in patients with SZ or BD were behaviorally evaluated using the Effort Expenditure for Rewards Task (EEfRT)<sup>28</sup> and MATRICS Cognitive Consensus Battery (MCCB)<sup>29</sup>, respectively.

To achieve our study objectives, we administered the CAINS and evaluated the relationship among neuroimaging (i.e., subcortical volumes) and behavioral (EEfRT and MCCB scores) measures with the overall negative symptom severity as well as specific domains of the CAINS (i.e., Motivation & Pleasure subscale, for which higher scores indicate greater severity of avolition, anhedonia and asociality; and the Expression subscale, for which higher scores indicate more problems with flat affect and alogia). Moreover, prior work has shown that reward/anti-reward, affective, and cognitive mechanisms are functionally regulated with the cerebellum and altered in psychotic illnesses<sup>4, 30-33</sup>, with output projections occurring among the cerebellum and classical reward-related CNS regions (i.e., striatum)<sup>34-36</sup>. We sought to determine whether and how negative symptom severity and related constructs (i.e., deficits in reward-motivation or cognition) were commonly represented in the CNS, including in subcortical and cerebellar regions. Defining the neural substrates associated with behavioral

performance on reward-motivation and cognitive tasks in SZ and BD may provide transdiagnostic and neurobiological insights into two core features of psychotic disorder that remain difficult to treat.

## **Materials and Methods**

### Study Participants

The study enrolled participants between 18 and 50 years old with a Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) diagnosis of a schizophrenia spectrum disorder (SZ) such as schizophrenia, schizoaffective disorder, or schizophreniform disorder or bipolar I disorder (BD) with psychotic features. Age and sex-matched healthy controls (HC) without psychiatric illness nor first-degree relatives with a psychotic disorder were also enrolled. Study participants with MRI contraindications, who were pregnant or nursing, or with active substance use were excluded from this study. All study procedures were approved by the MGB Institutional Review Board (IRB) and the Boston Children's Hospital IRB. All participants provided written informed consent.

### Clinical Assessments

All study participants underwent the *Structured Clinical Interview for DSM-5 (SCID-5)* to confirm diagnoses of SZ and BD, as well as absence of psychiatric disorders in HCs. For patients with SZ or BD, we administered the *Clinical Assessment Interview for Negative Symptoms (CAINS)* and the *Young Mania Rating Scale (YMRS)* to evaluate negative and manic symptoms, respectively<sup>1,36,37</sup>, as well as the *Positive and Negative Syndrome Scale (PANSS)*, a 30-item clinical assessment for positive symptoms, negative symptoms, and general psychopathology. Additionally, the Montgomery-Åsberg Depression Rating Scale

(MADRS) and Beck Depression Inventory (BDI) were used to assess depressive symptoms<sup>38,39</sup>, while the Hamilton Anxiety Rating Scale (HAM-A) was used to evaluate anxiety symptoms<sup>40</sup>.

### Neuroimaging Acquisition

All MRI data were acquired at McLean Hospital on a Siemens 3T Prisma scanner with a 64-channel head coil. Protocols for high-resolution anatomical, diffusion tensor imaging (DTI), and resting-state functional MRI (fMRI) scans were adapted from the Human Connectome Project and utilized identical scanning parameters<sup>41</sup>. High-resolution anatomical, multi-echo magnetization-prepared rapid acquisition with gradient echo images were collected to assess gray matter morphological properties: 1mm<sup>3</sup>, TR= 2.53s, TE1=1.69ms, TE2=3.55ms, TE3=5.41ms, TE4=7.27ms, GRAPPA=2, 128 slices. DTI was acquired to assess white matter (WM) integrity and interregional structural connectivity with the following parameters: TR: 3230ms, TE: 89.20ms, 1.5mm isotropic, GRAPPA=2, MB=4, b=3000s/mm<sup>2</sup>, 99 directions, 92 slices. Resting-state fMRI data was collected to measure functional connectivity with the following parameters: gradient echo T2\*-weighted echo-planar images were acquired using a multi-band sequence with 2 mm<sup>3</sup> resolution: TR/TE=800ms/37ms, 72 slices, GRAPPA=2, multiband factor=8. Study participants were asked to remain awake with their eyes open for a 7-minute period during which time no task or stimulation was administered.

### Neuroimaging Analysis

*Gray matter morphological analysis:* MPRAGE images underwent the FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>) recon-all pipeline for morphometric analysis of (sub)cortical brain structures, i.e., cortical thickness and gray matter volumes<sup>42</sup>. The Destrieux atlas<sup>43</sup> was adopted for cortical segmentation into 148 anatomical regions of interest (ROIs) and the Automatic Segmentation of Subcortical Structures (ASEG) atlas<sup>44</sup> was implemented for subcortical segmentation into 40 ROIs.

To examine structural properties with the cerebellum, an optimized voxel-based morphometry (VBM) of infratentorial structures was performed using the Spatially Unbiased Infratentorial Template (SUIT) toolbox within Statistical Parametric Mapping (SPM12). The workflow encompassed the following steps: visual inspection of images, alignment to the anterior commissure, segmentation of the cerebellum and brainstem, manual adjustments, normalization and reslicing to the SUIT template, and Jacobian modulation for volumetric analysis. A Gaussian smoothing kernel with a 2 mm full width at half maximum (FWHM) was applied to the data. Voxel-based analyses employed an ANOVA test in SPM12, adjusting for sex, age, and total intracranial volume. Resulting statistical maps were thresholded at  $z = 3.1$  ( $p = 0.001$ ). A FAMILY-WISE ERROR RATE OF  $P = 0.05$  was applied to correct for multiple comparisons.

*White matter structural analysis:* DTI analysis was first carried out using tract-based spatial statistics (TBSS) in FMRIB Software Library (FSL) ([www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). Each DTI dataset was corrected for eddy-current distortion and head motion using an automated affine registration algorithm with the skull-stripped structural image as the reference volume. Least squares fit of the tensor model was employed to calculate a diffusion tensor for each voxel and the eigenvalues of each tensor, representing the diffusion directions, and fractional anisotropy (FA) values were calculated. FA values of white matter pathways and for each study participant were extracted by co-registration of FA maps to a template brain, where pathways of interest were defined by the JHU white matter atlas. Cerebellar white matter pathways, left and right hemispheres separately, analyzed in each DTI dataset consisted of the inferior, middle, and superior cerebellar peduncles.

*Resting-state functional connectivity analysis:* Whole-brain ROI-to-ROI (i.e., nucleus accumbens and cerebellar sub-divisions) correlation functional connectivity analysis was performed using the CONN-fMRI fc toolbox v18.b<sup>45</sup> in conjunction with SPM 12 (<http://www.fil.ion.ucl.ac.uk/spm/>) using default

parameters and a combination of the Harvard-Oxford atlas and an imported cerebellar mask based on a cluster in lobule VI showing significant inter-cohort morphological differences (i.e., SZ vs. BD)<sup>46</sup>.

### Effort Expenditure for Rewards Task (EEfRT)

The EEfRT<sup>27</sup> is a computerized task that enables an objective determination of reward-related motivational deficits<sup>47,48</sup>. Participants are given a probability (12%, 50%, or 88%) of receiving a hypothetical monetary reward, and then must choose between three levels of task difficulty (i.e., easy, medium, and hard). Successful completion of easy trials requires 30 button presses using the dominant index finger within 7s, while successful completion of hard trials requires participants to make 100 button presses with their non-dominant pinky finger within 21s<sup>27</sup>. Both the magnitude and probability of receiving the monetary rewards upon completion are varied. Studies have demonstrated that patients with psychosis do not allocate as much effort as HC as either reward magnitude or probability increase<sup>49- 53</sup>, and that such impaired decision-making is associated with more severe negative symptoms<sup>49,51</sup>, amotivation<sup>53,54</sup>, and functional impairments<sup>51,53</sup>. The EEfRT probability index, in particular, has been shown to have good external validity with negative symptom scales<sup>55</sup> and good psychometric properties<sup>50,56</sup>.

### Cognitive Assessments

The MATRICS Cognitive Consensus Battery (MCCB)<sup>28</sup> was administered to evaluate seven domains of cognitive functioning, including processing speed, attention, working memory, verbal learning, visual learning, problem solving, and social cognition. Scores were age, sex, and education level-normed using the MCCB scoring software.

### Statistical Analysis

Demographic and clinical symptom scores were compared between HC, SZ, and BD cohorts using Kruskal-Wallis tests. A two-tailed p-value of < 0.05 was considered significant. Neuroimaging endpoints were compared between cohorts using multivariate analyses of covariance (MANCOVAs) with age, sex, and total intracranial volume as covariates for subcortical volumes (nucleus accumbens) and age and sex as covariates for DTI-based measures. To correct for multiple comparisons, adjusted p-values were calculated and controlled for the false discovery rate (FDR;  $\alpha = 0.05$ ). Note, in SUIT, a default FWE ( $P = 0.05$ ) procedure was utilized to correct for multiple comparisons. A two-tailed p-value of < 0.05 was considered significant. Pearson correlation analyses were performed to determine associations between neuroimaging endpoints, behavioral endpoints, and scores on clinical instruments (i.e., CAINS total score, CAINS Motivation and Pleasure subscale score, CAINS Expression subscale score; see also **Table 1**). P-values of correlations were adjusted using an FDR ( $\alpha = 0.05$ ) correction.

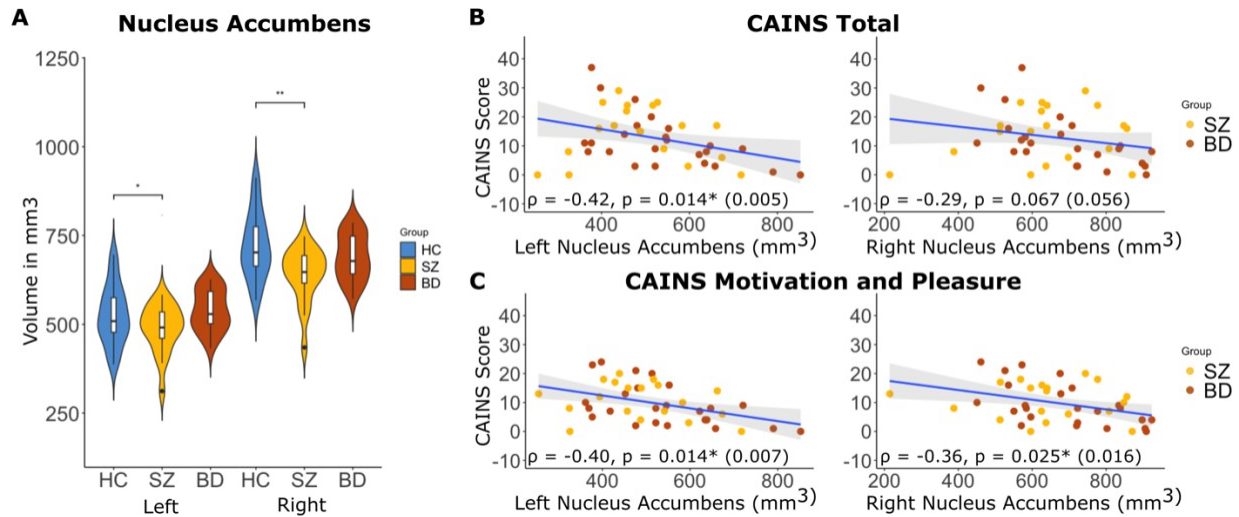
## **Results**

### Study Participants

44 adult patients with psychosis (SZ = 20, BD = 24) and 27 HCs were enrolled in this prospective study. Demographic and clinical characteristics of the three study cohorts are provided in **Table 1**. There were no significant differences in age between HCs, patients with SZ, and patients with BD. A chi-square test of independence showed no significant association between group and gender distribution ( $\chi^2(2, N = 72) = 4.56, p = 0.10$ ). Negative symptom severity as measured by the CAINS total and subscale scores were similar between SZ and BD cohorts. The overall severity of psychotic symptoms (PANSS), mania (YMRS), depression (MADRS and BDI), and anxiety (HAMA) was also comparable between patients with SZ and patients with BD.

### Reduction in Nucleus Accumbens Volume in Patients with Psychosis

Multivariate analysis showed significant differences in nucleus accumbens volume (left:  $F(2, 64) = 3.670$ ,  $p = 0.088$ ; right:  $F(2, 64) = 3.823$ ,  $p = 0.027$ ) across the three participant groups (**Fig. 1A**). Post-hoc pairwise comparisons revealed that both the left and right nucleus accumbens were reduced in patients with SZ compared to HC (left:  $p(\text{corrected}) = 0.048$ ; right:  $p(\text{corrected}) = 0.010$ ). In the combined psychosis group (SZ + BD) the volume of the nucleus accumbens negatively associated with negative symptom severity (**Fig. 1A-1B**). The volume of the nucleus accumbens was negatively correlated with the CAINS Total score (left:  $r = -0.42$ ,  $p(\text{corrected}) = 0.014$ , right:  $r = -0.29$ ,  $p(\text{corrected}) = 0.067$ ). This correlation was particularly robust when determining the relationship between nucleus accumbens volumes and CAINS Motivation and Pleasure subscale scores (left:  $r = -0.43$ ,  $p(\text{corrected}) = 0.022$ , right:  $r = -0.38$ ,  $p(\text{corrected}) = 0.042$ ). Neither the CAINS Expression subscale nor YMRS scores were not significantly correlated with left and right nucleus accumbens volumes. Significant volumetric differences in other subcortical structures were not observed across the three participant groups. Cortical thickness values in the right inferior orbital frontal gyrus was significantly greater in patients with SZ relative to patients with BD ( $p = 0.03$ ). However, significant correlations between cortical thickness of the right inferior orbital frontal gyrus and CAINS total or subscale scores were not present.

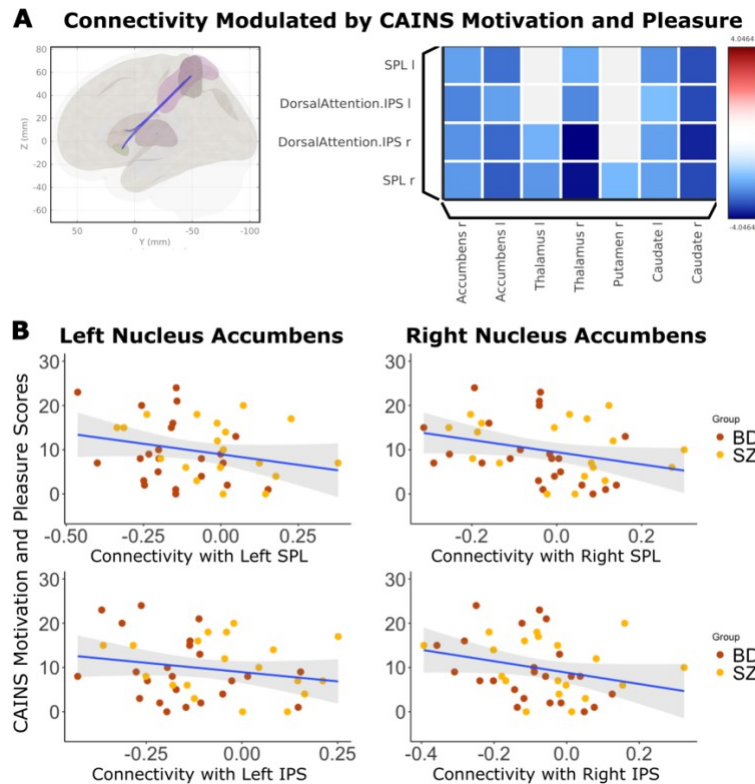


**Figure 1. Associations between nucleus accumbens volume and negative symptom severity. A.** Relative to HCs, significantly reduced bilateral nucleus accumbens volume was present in patients with SZ. The nucleus accumbens was defined using the Destrieux atlas. Between group statistical comparisons were performed with Analyses of Covariance (FDR corrected two-tailed p-values,  $\alpha = 0.05$ ) using age, sex, and intracranial volume as covariates. \* $p < 0.05$ , \*\* $p < 0.001$ . **B.** A trend of lower nucleus accumbens volume (left and right) and higher CAINS Total scores was detected in patients with psychosis (SZ+BD). Significant associations of lower nucleus accumbens volume (left and right) and higher CAINS Motivation and Pleasure subscale scores was detected in patients with psychosis (SZ+BD). Pearson's  $r$  values and FDR-corrected p-values are reported, with p-values uncorrected for multiple comparisons reported in parentheses. Shaded areas on correlation plots indicate 95% confidence interval.

### Decreased Nucleus Accumbens Functional Connectivity and its Associations with Negative Symptoms

A whole brain ROI-to-ROI resting-state functional connectivity analysis was performed with CAINS Total and subscale scores set as covariates of interest. Age and gender were also included as regressors. Lower functional connectivity between the left and right nucleus accumbens with the intraparietal sulcal division of the dorsal attention network (left and right) as well as the superior parietal lobe was significantly associated with higher CAINS Motivation and Pleasure subscale scores only ( $F(2, 37) = 12.68$ ,  $p(\text{uncorrected}) < 0.0001$ ,  $p(\text{corrected}) = 0.034$ ) (**Fig. 2A**). Individual associations between connectivity of the left and right nucleus accumbens with the parietal regions and CAINS Motivation and Pleasure subscale scores ranged from  $r = -0.25$  to  $-0.29$  (**Fig. 2B**). Overlapping functional connectivity findings involving the dorsal striatum (left caudate, right caudate, and right putamen) and left and right thalamus were also observed (i.e., lower functional connectivity and higher CAINS Motivation and

Pleasure scores). In patients with SZ and BD, no significant associations were observed between nucleus accumbens-based functional connectivity strengths and MADRS, BDI, and HAMA scores, each of which was set as a covariate of interests in independent analysis.

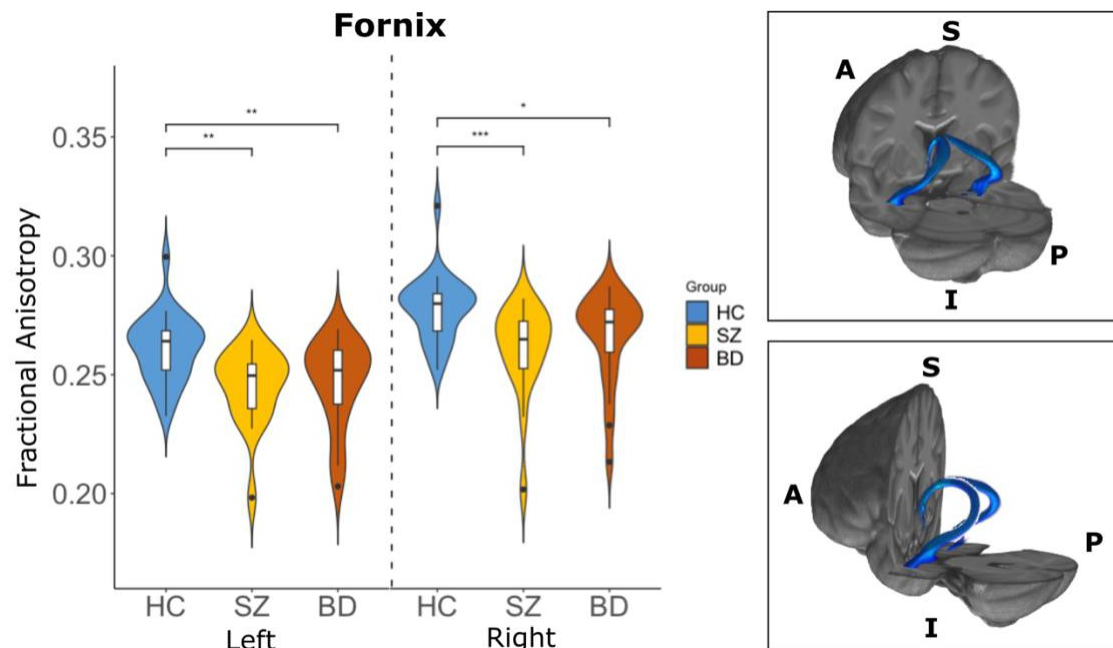


**Figure 2. Nucleus accumbens connectivity modulated CAINS Motivation and Pleasure subscale scores.** **A.** Cluster-level connectivity alterations were found between the nucleus accumbens and parietal regions (intraparietal sulcus and superior parietal lobule) when using the CAINS Motivation and Pleasure subscale as a regressor. **B.** Associations of the connectivity of left and right nucleus accumbens and intraparietal sulcus and superior parietal lobule with the CAINS Motivation and Pleasure subscale scores ranged from  $r = -0.25$  to  $-0.29$ .

### Reduced FA in the Fornix in Patients with Psychosis

The fornix is a white matter pathway integrated with the limbic and mesocorticolimbic systems and a component of the Papez circuit<sup>57,58</sup>. White matter fibers of the fornix project between the nucleus accumbens, hippocampus, and forebrain. Both patients with SZ as well as patients with BD showed

reduced FA in the left and right fornix compared to HC (**Fig. 3**). Similar to the trend in nucleus accumbens volume, the SZ cohort (vs. HCs and vs. patients with BD) demonstrated the lowest FA value in left and right fornix. In the BD cohort, the right fornix FA values showed a negative correlation BDI scores:  $r = -0.45$ ,  $p(\text{uncorrected}) = 0.036$ ,  $p(\text{corrected}) = 0.059$ , while the left fornix FA values demonstrated a negative correlation with HAMA scores:  $r = -0.46$ ,  $p(\text{uncorrected}) = 0.030$ ,  $p(\text{corrected}) = 0.05$ . Significant correlations among fornix FA values and all other clinical scores or subscale scores were not observed.

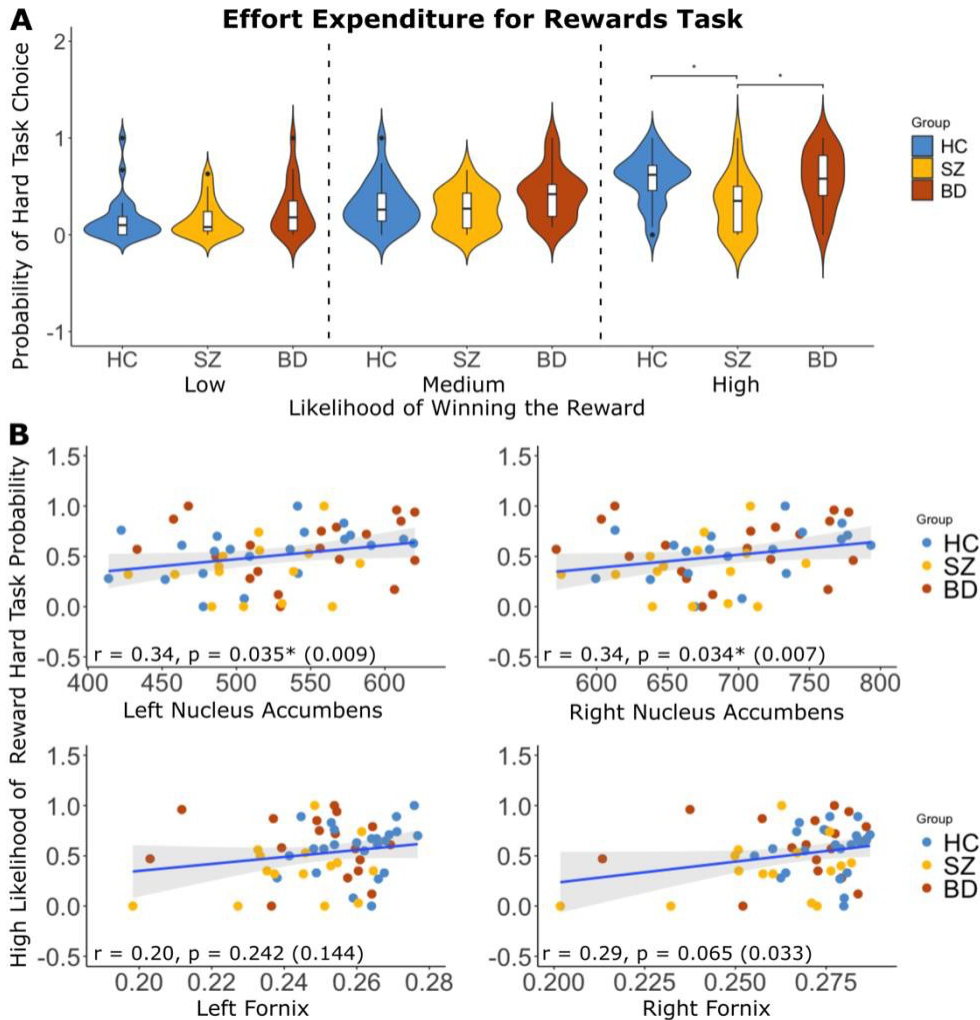


**Figure 3. Reduced fractional anisotropy (FA) of the fornix in patients with psychosis. A.** Relative to HCs, both SZ and BD cohorts showed reduced FA in the left and right fornix. The fornix was defined using the JHU-DTI atlas. Between group statistical comparisons were performed with Analyses of Covariance using age and sex as covariates (FDR corrected two-tailed  $p$ -value,  $\alpha = 0.05$ ). \* $p < 0.05$ , \*\* $p < 0.001$ , \*\*\* $p < 0.001$ .

### Neural Correlates of Reward-Related Motivational Deficits

Multivariate tests indicated a significant effect of cohort across the dependent variables, Pillai's trace = 0.233,  $F(6, 108) = 2.37$ ,  $p = 0.034$  (**Fig. 4A**). Univariate tests revealed a significant group effect during a high likelihood of a reward,  $F(2, 55) = 4.83$ ,  $p = 0.012$ , with post-hoc pairwise comparisons showing that the SZ cohort had significantly lower probabilities of choosing the hard task as compared to HCs ( $p(\text{corrected}) = 0.022$ ) and BD patients ( $p(\text{corrected}) = 0.021$ ). No significant differences were found for low or medium likelihoods of reward (all  $p > 0.05$ ).

The left ( $r = 0.34$ ,  $p(\text{corrected}) = 0.035$ ) and right ( $r = 0.34$ ,  $p(\text{corrected}) = 0.034$ ) nucleus accumbens show significant associations with lower expenditure of effort for the high reward probability condition (**Fig. 4B**). A trend of lower FA values in the fornix and lower expenditure of effort for the high reward probability task was also observed (**Fig. 4C**). In the SZ cohort, expenditure of effort during high reward probability associated with higher MADRS scores ( $r = 0.57$ ,  $p(\text{uncorrected}) = 0.017$ ,  $p(\text{corrected}) = 0.15$ ). Significant correlations between expenditure of effort during high reward probability and all other clinical scores or subscale scores were not observed.



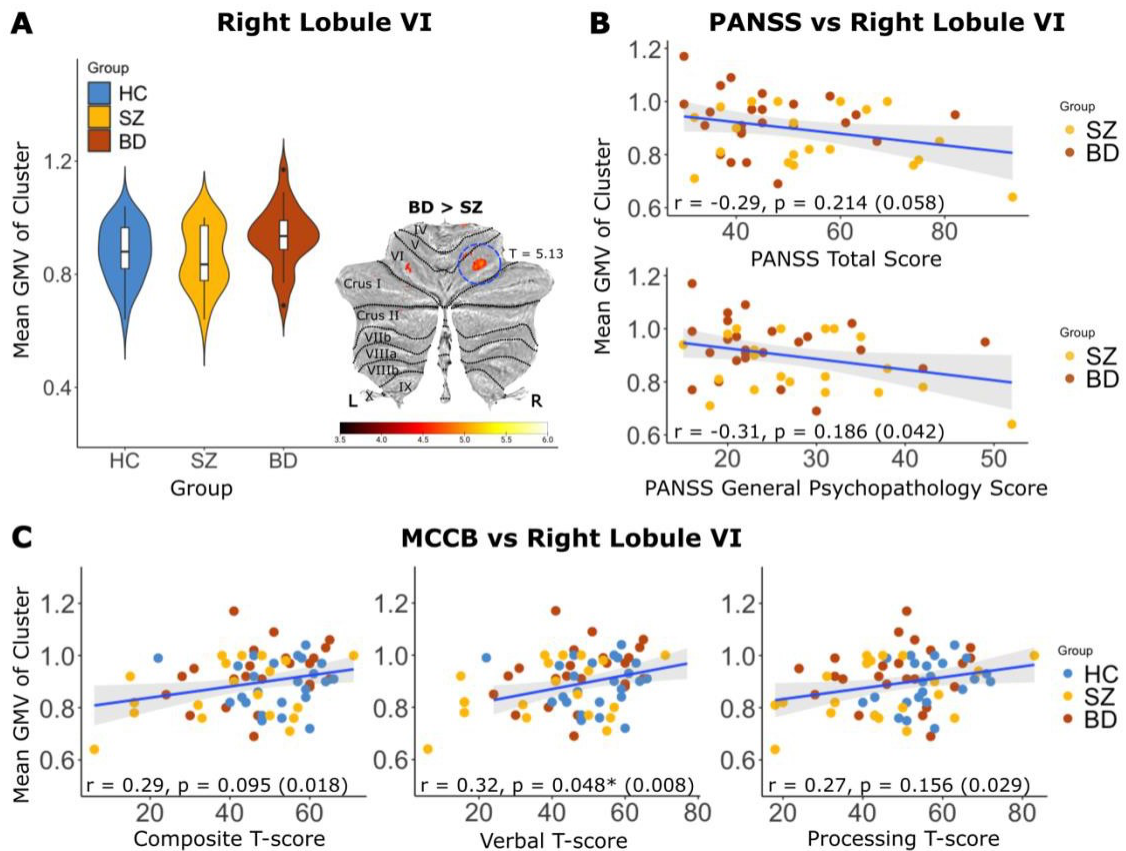
**Figure 4. Reward-related motivational deficits and their associations with negative symptom severity in psychosis. A.** The Effort-Expenditure for Rewards Task (EEfRT) was administered to determine reward-related motivational deficits in SZ and BD cohorts. Comparable effort expenditure was observed among HCs, patients with SZ, and patients with BD when the probability of reward was low or medium. However, significant deficiency in reward-related motivation in patients with SZ was observed when the probability of reward was high. Patients with SZ expended significantly less effort compared to HCs and patients with BD. Between group statistical comparisons were performed with Mann-Whitney U tests (FDR corrected two-tailed p-value,  $\alpha = 0.05$ ). \* $p < 0.05$  **B.** A lower expenditure of effort for the high reward probability task associated with smaller left and right nucleus accumbens volumes. A trend of lower expenditure of effort for the high reward probability condition and lower left and right fornix FA values was observed. Pearson's  $r$  values and FDR-corrected p-values are reported, with p-values uncorrected for multiple comparisons reported in parentheses. Shaded areas on correlation plots indicate 95% confidence interval.

## Cognitive Deficits in Psychosis and their Relationships with Cerebellar Morphological Changes

Overall, patients with SZ demonstrated more cognitive deficits relative to HCs and patients with BD (**Table 2**). Across the three cohorts, significant differences were present for the MCCB (i) Speed of processing sub-score, (ii) Verbal learning and memory sub-score, (iii) Visual learning and memory sub-score, and (iv) Composite score. Relative to patients with BD, patients with SZ showed poorer performance in the verbal learning and memory ability ( $p = 0.01$ ), while performance in all other MCCB domains was comparable between SZ and BD cohorts. A significant negative correlation was observed between the MCCB Verbal learning and memory sub-score and the CAINS Motivation and Pleasure subscale score ( $r = -0.45$ ,  $p(\text{corrected}) = 0.012$ ) as well as between the MCCB Composite score and CAINS Motivation and Pleasure subscale score ( $r = -0.37$ ,  $p(\text{corrected}) = 0.040$ ).

Through VBM analysis, altered morphological differences in cerebellar subdivisions across HCs, patients with SZ, and patients with BD were observed (**Fig. 5A**). In parallel with morphological changes involving the nucleus accumbens (**Fig. 1A**), patients with SZ showed the smallest cerebellar volumes in lobule VI. The cluster survived family-wise error correction ( $p\text{FWE} < 0.0001$ ) with a size of 94 voxels. At the peak, the analysis revealed a T-value of 5.13 ( $p\text{FWE} = 0.026$ ) at MNI coordinates (27, -65, -24). Cerebellar subdivisions showing volumetric decreases did not correlate with the severity of negative symptoms or mania; however, a trend of smaller lobule VI volumes associated with higher PANSS total or PANSS general psychopathology score in the combined SZ + BD cohort (**Fig. 5B**). Additionally, significant relationships between cerebellar volumes and reward-related motivational deficits (EEfRT) were absent; however reduced volumes in lobule VI corresponded with poorer performance on the MCCB. Lower MCCB scores on the Verbal learning and memory sub-score significantly correlated with lobule VI cluster volume in the combined SZ + BD cohort ( $r = 0.32$ ,  $p(\text{corrected}) = 0.048$ ). No significant correlations with lobule VI were found for the SZ or BD cohorts individually (**Table 3**).

No significant group differences in FA were found for the inferior (left:  $F(2, 63) = 1.377, p = 0.260$ ; right:  $F(2, 63) = 1.749, p = 0.182$ ), middle ( $F(2, 63) = 1.635, p = 0.203$ ), and superior (left:  $F(2, 63) = 2.285, p = 0.110$ ; right:  $F(2, 63) = 0.917, p = 0.405$ ) cerebellar peduncles. Functionally, no group differences in resting-state connectivity were found with the imported cerebellar mask of lobule VI nor the default atlas-defined lobule VI ROI (HC vs SZ vs BD and HC vs SZ+BD;  $p < 0.05$  cluster FDR-corrected,  $p < 0.05$  uncorrected connection threshold, MVPA omnibus test) with other ROIs or variables of interest including PANSS, CAINS, or MCCB (sub-)scores.



**Figure 5. Morphological alterations in cerebellar subdivisions and their associations with cognitive deficits. A.** VBM analysis of the cerebellum showed reduced volumes in patients with SZ relative to HCs and patients with BD. Cerebellar VBM was performed using the Spatially Unbiased Infratentorial Template (SUIT) toolbox within Statistical Parametric Mapping (SPM12). Regions of reduced cerebellar volume (red-yellow clusters) in the SZ cohort were observed in lobule V, lobule VI, crus I, and crus II, but only the cluster in lobule VI survived a voxel threshold of 20

voxels. Statistical maps were thresholded at  $z = 3.1$  ( $p = 0.001$ ). A family-wise error (FWE) rate of  $p = 0.05$  was applied to correct for multiple comparisons. **B.** Morphological changes in cerebellar subdivisions in the psychosis cohort (SZ + BD) were not associated with negative symptoms (defined by CAINS Total or sub-scale scores). However, a trend of lower cerebellar volumes was associated with PANSS General Psychopathology score. Pearson's  $r$  values and FDR-corrected  $p$ -values are reported, with  $p$ -values uncorrected for multiple comparisons reported in parentheses. **C.** Significant associations between cerebellar volume reduction and reward-related motivational deficits (EEfRT) were not identified. However, more reduced volumes within cerebellar subdivisions were associated with reduced cognitive ability (MATRICS Consensus Cognitive Battery), particularly in the verbal learning and memory domain, while a trend among cerebellar volumes and the composite scores and processing speed was present. Pearson's  $r$  values and FDR-corrected  $p$ -values are reported, with  $p$ -values uncorrected for multiple comparisons reported in parentheses.

## Discussion

Negative symptoms are highly prevalent among individuals affected by psychotic disorders, including SZ and BD<sup>2,5</sup>. Despite advances in the treatment of positive symptoms using dopamine-blocking antipsychotic medications, negative symptoms and cognitive impairments often persist beyond remission of positive symptoms, presenting a significant challenge in the management of psychosis<sup>17,18</sup>. Recent evidence suggests that an  $M_1$  / $M$ . preferring muscarinic receptor agonist may help alleviate negative symptoms independently of the effects on positive symptoms<sup>61</sup>. Neuroimaging has become instrumental in identifying neural circuitry associated with negative symptoms, revealing both morphological changes and functional disruptions in regions like the ventral and dorsal striatum, frontal cortices, amygdala, hippocampus, and cerebellar subdivisions<sup>4,22,32</sup>. These findings have been contextualized within frameworks of emotional dysregulation, reward anticipation, and the encoding of positive and negative valence<sup>22,23</sup>. Such insights suggest that negative symptoms may arise from complex alterations within a network of brain regions involved in motivation, reward processing, and emotion regulation. The present study aimed to identify biobehavioral markers related to negative symptoms and cognitive impairments in psychosis, specifically within SZ and BD patients with psychotic features. We postulated that in psychotic illnesses, negative symptoms and cognitive impairment may be driven by shared pathophysiological mechanisms (e.g., dopamine dysfunction) and relatedly, implicate parallel CNS networks (e.g.,

mesocorticolimbic pathways)<sup>22,27</sup>, and therefore, these two core features of psychosis may be monitored by overlapping neuroimaging biomarkers. Yet, our findings indicate that while nucleus accumbens-based measures may serve as transdiagnostic markers of negative symptoms and deficits in reward-motivation, morphological properties of cerebellar lobule VI align more with cognitive performance.

We observed significant reductions in the volume of the nucleus accumbens of patients with SZ, which were associated with greater negative symptom severity as indicated by CAINS Motivation and Pleasure subscale scores. The significant association between reduced nucleus accumbens volume and decreased effort expenditure during high-reward probability tasks (EEfRT) further underscores the relevance of this region to motivational deficits. These results are consistent with prior research demonstrating that the nucleus accumbens is involved in impaired reward processing in psychosis<sup>62</sup>.

Resting-state functional connectivity analyses extended these findings by showing reduced connectivity between the nucleus accumbens and regions of the parietal cortex, specifically the intraparietal sulcus and superior parietal lobule. This disruption in connectivity was linked to more severe motivational and pleasure deficits. The intraparietal sulcus is implicated in attention, working memory, nonspatial manipulation (i.e., arithmetic) and cognitive control<sup>63</sup>, which may explain how disrupted connectivity with the nucleus accumbens contributes to the reduced ability of patients with SZ to exert effort in response to rewards.

While the fornix, a white matter tract connecting the nucleus accumbens with the hippocampus and other limbic structures, showed reduced fractional anisotropy in patients with psychosis, no direct correlations were observed between fornix integrity and negative symptom severity. However, the trend of reduced fornix integrity aligning with lower effort expenditure in the high-reward condition suggests that disruptions in this white matter pathway may still play a role in motivational impairments in psychosis.

Interestingly, recent work reported decreased fornix volume in patients with major depressive disorder (MDD), with more robust volumetric reductions in the fornix in MDD patients with anhedonia<sup>64</sup>.

In addition to the nucleus accumbens, bilateral morphological alterations were observed in lobule VI of the cerebellum, where volume loss was more substantial in the SZ cohort relative to HCs and patients with BD. While this volumetric trend paralleled those made in the nucleus accumbens, the associations with other study measures differed substantially. For instance, significant correlations with CAINS total or subscales scores or EffRTS based measures and lobule VI volume. However, lower lobule VI volumes trended with higher scores on PANSS total and PANSS general psychopathology sub-scores. The lack of significant differences in cerebellar peduncle integrity or resting-state functional connectivity with cerebellar lobule VI suggests that cerebellar contributions to cognitive impairments in psychosis may be more related to local gray matter structural changes rather than white matter pathways or broader network connectivity.

The functional role of lobule VI is distributed across multiple domains. Lobule VI is implicated in sensorimotor, working memory, cognitive, and affective processes; mechanisms likely regulated in part by dopaminergic signalling<sup>65-67</sup>. Relatedly, a recent preclinical study further highlighted dopaminergic mediated mechanism of action integrated within lobule VI, which was proposed to facilitate reward processing, addictive behaviors, and motor coordination<sup>68</sup>. In clinical populations, a functional segmentation of the right lobule VI confirms its overall involvement in sensorimotor processing but more specifically, its role in reading, speech production, and visual processing<sup>65</sup>. In patients with Niemann Pick Disease Type C, a progressive neurodegenerative condition with neuropsychiatric symptom presentation, volumetric loss in lobule VI and reduced functional activity during speech production has been observed<sup>69</sup>. The current morphological findings in the right lobule VI cerebellum in conjunction with significant

correlations among lobule VI and verbal learning performance (via MCCB) provide additional insights into lobule VI's functionality, but also, how this subdivision is modulated across patients with SZ or BD.

Overall, these results contribute to a growing body of research suggesting that the neural substrates of psychosis involve distinct but overlapping circuits related to motivation, reward processing, and cognitive function. The nucleus accumbens appears to play a central role in the motivational deficits observed in SZ and BD, while cerebellar subdivisions, particularly lobule VI, are more closely tied to cognitive impairments. This study also has several limitations. One, larger samples are needed to confirm the observed associations, whether in relation to negative symptom severity, reward-motivation deficits, or cognitive impairments. The present cross-sectional study design prohibits conclusions to be made regarding the dynamics of the brain-behaviour relations described herein. Furthermore, the reliance on self-report measures for psychiatric symptoms may potentially influence the accuracy of the reported data. Moreover, the inclusion of only adult participants in this study limits our understanding of the developmental trajectories of psychotic disorders and their neurobiological underpinnings. To expand on the limitations of our assessment measures, future studies may consider using both the Snaith-Hamilton Pleasure Scale (SHAPS) and the Hamilton Depression Rating Scale (HAM-D) alongside the Monetary Incentive Delay (MID) task<sup>35,70</sup>. This combination would allow for a more refined examination of consummatory and anticipatory anhedonia, which may differentiate aspects of reward processing and motivation across psychotic disorders. Despite these limitations, this study underscores the importance of developing targeted interventions that can modulate both reward-related circuits and cerebellar function. Such approaches could lead to improved therapeutic outcomes for patients with psychosis, potentially enhancing motivation, cognitive function, and overall quality of life. Further research is needed to refine these strategies and explore their clinical applications, ultimately contributing to a more

comprehensive understanding of the neurobiological underpinnings of psychosis in a broader spectrum of patients and conditions.

## **Conclusion**

This study provides evidence that structural and functional changes in the nucleus accumbens and cerebellum are associated with negative symptoms and cognitive impairments in SZ and BD. The findings suggest that reduced nucleus accumbens volume is closely linked to motivational deficits, while cerebellar alterations, particularly in lobule VI, are related to cognitive impairment. These results underscore the importance of targeting both reward-related circuits and cerebellar function in developing interventions for psychosis. Future research should include larger cohorts and longitudinal designs to further clarify the temporal relationships between these neural changes and negative symptom progression.

**Table 1. Demographics and clinical questionnaire responses.**

<b>Demographics (Male/Female)</b>	<b>HC (14/13)</b>	<b>SZ (15/5)</b>	<b>BD (11/14)</b>	<b>P-value</b>
Age in years	30.1 ± 9.4	32.7 ± 9.1	30.8 ± 9.3	0.53
<b>CAINS</b>				
Total	-	14.0 ± 9.3	11.7 ± 9.1	0.39
Motivation and Pleasure	-	10.5 ± 6.2	9.2 ± 7.3	0.49
Expression	-	4.2 ± 4.6	2.5 ± 3.6	0.30
<b>YMRS</b>	-	9.4 ± 8.7	6.2 ± 7.8	0.22
<b>PANSS</b>				
Total	-	55.0 ± 16.7	46.0 ± 12.2	0.06
General Psychopathology	-	28.5 ± 9.1	25.0 ± 8.1	0.17
Positive	-	12.0 ± 5.2	9.3 ± 3.3	0.07
Negative	-	14.5 ± 5.4	11.7 ± 3.8	0.12
<b>MADRS</b>	-	12.7 ± 9.5	13.5 ± 11.6	0.67
<b>BDI</b>	-	9.5 ± 9.6	11.5 ± 10.3	0.68
<b>HAMA</b>	-	10.6 ± 8.8	11.7 ± 10.0	0.99

*BD bipolar disorder, SZ schizophrenia, CAINS Clinical Assessment Interview for Negative Symptoms, YMRS Young Mania Rating Scale, PANSS Positive and Negative Syndrome Scale, MADRS Montgomery-Åsberg Depression Rating Scale, BDI Beck Depression Inventory, HAMA Hamilton Anxiety Rating Scale. Data are presented as mean score ± standard deviation. Statistical analysis was performed using Mann-Whitney U-Tests and Kruskal-Wallis tests as appropriate.*

**Table 2. MATRICS battery subscales and composite score.**

<b>MATRICS Battery</b>	<b>HC</b>	<b>SZ</b>	<b>BD</b>	<b>P(uncorrected)</b>	<b>P(corrected)</b>
Processing	55.3 ± 9.1	44.6 ± 16.9	49.3 ± 12.7	<b>0.02</b>	<b>0.04</b>
Attention	46.6 ± 9.3	40.4 ± 13.3	42.3 ± 10.9	0.14	0.22
Memory	49.6 ± 9.6	43.9 ± 13.6	50.5 ± 8.6	0.27	0.36
Verbal	52.9 ± 11.3	40.7 ± 11.7	52.6 ± 11.5	<b>&lt;0.01</b>	<b>0.03</b>
Visual	52.6 ± 11	38.8 ± 14.9	45.3 ± 10.3	<b>&lt;0.01</b>	<b>0.03</b>
Solving	50.8 ± 11.0	47.6 ± 12.6	51.2 ± 7.7	0.65	0.65
Social	52.2 ± 11.3	48.0 ± 15.9	49.6 ± 11.6	0.34	0.39
Composite	52.3 ± 10.6	39.2 ± 17.6	47.7 ± 11.9	<b>0.01</b>	<b>0.03</b>

MATRICS Cognitive Consensus Battery (MCCB). Data are presented as mean score ± standard deviation. Statistical analysis was performed using Kruskal-Wallis tests and corrected for multiple comparisons using FDR.

**Table 3. Associations between lobule VI and clinical variables for SZ and BD groups separately.**

<b>SZ</b>			
<b>Measure</b>	<b>Pearson r</b>	<b>P(uncorrected)</b>	<b>P(corrected)</b>
<b>CAINS</b>			
Total	0.11	0.66	0.87
Motivation and Pleasure	-0.14	0.59	0.87
Expression	0.07	0.76	0.87
<b>PANSS</b>			
Total	-0.30	0.20	0.60
General Psychopathology	-0.38	0.10	0.60
Positive	<0.01	1.00	1.00
Negative	-0.28	0.23	0.60
<b>EEfRT</b>			
High Probability of Reward	0.22	0.40	0.81
<b>BD</b>			
<b>Measure</b>	<b>Pearson r</b>	<b>P(uncorrected)</b>	<b>P(corrected)</b>
<b>CAINS</b>			
Total	-0.26	0.22	0.87
Motivation and Pleasure	-0.37	0.08	0.64
Expression	0.07	0.74	0.94
<b>PANSS</b>			
PANSS Total	-0.12	0.57	0.94
PANSS General Psychopathology	-0.15	0.49	0.94
PANSS Positive	0.02	0.92	0.94
PANSS Negative	-0.10	0.66	0.94
<b>EEfRT</b>			
High Probability of Reward	-0.02	0.94	0.94

*BD* bipolar disorder, *SZ* schizophrenia, *CAINS* Clinical Assessment Interview for Negative Symptoms, *PANSS* Positive and Negative Syndrome Scale, Multiple comparisons corrections were performed using FDR.

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