Effects of Cannabis for Persons with Schizophrenia: Implications for Reward Processing

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Abstract

Deficits in reward processing have been observed for patients with Schizophrenia paralleled by alterations in brain circuitry underlying reward behaviors. Cannabis is posited to increase reward sensitivity in chronic users. However, the effects of cannabis on reward processing for persons with comorbid cannabis use disorder and Schizophrenia remain unclear. To address this, I compared performance in reward behaviors and resting-state brain networks in a group of patients with Schizophrenia vs. adults without Schizophrenia or cannabis use disorder. In patients, I examine behavioral responses before and after cannabis use. Findings will more precisely characterize symptom dimensions for comorbid disorders.

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Background

Previous research has observed impairments of brain reward network activity for persons with comorbid Cannabis Use Disorder and Schizophrenia. Differences in reward processing remain an important dimension of psychotic disorders due to their relationship with negative symptoms. The present study aims to further characterize brain and behavioral implications of reward processing through analysis of experimental manipulation of cannabis to patients with Schizophrenia.

Reward in the Brain

The mesolimbic and mesocortical dopamine pathways are bidirectional projections to and from the nucleus accumbens (NAcc), and they are largely observed to facilitate reward processing (Haber & Behrens 2014).The nucleus accumbens shows activation in response to the anticipation of a reward or pleasurable stimuli, and activation in the region is flexible to maintain highest sensitivity to unexpected rewards (O'donnell et al. 1999; Schultz 2016). Dopamine is known to facilitate pleasurable sensations at the neurotransmitter level. Dopamine pathways in the brain are also integrated in motivational behaviors and have been implicated in movement as well as motor initiation (Collins & Frank 2016). These implications suggest that the nucleus accumbens facilitates learning of habitual behaviors especially in the context of motivation via dopamine.

As cortico-striatal interactions support reward processing (Haber 2016), changes in these neurobiological systems have been discussed as indicators for brain and cognitive function (Whitfield-Gabrieli et al. 2009). Functional connectivity (Biswal et al. 2010), or the temporal coactivation of neural regions, of basal ganglia regions between prefrontal and orbitofrontal

regions have been implicated in the maintenance of habitual behaviors and reward learning (Lutz & Widmer 2014). Additionally, value processing of rewards has been associated with dorsolateral prefrontal cortex and ventral striatum functional connectivity (Camara et al. 2009).

Schizophrenia and Reward Processing

Schizophrenia is a debilitating mental disorder typically characterized by disorganized thoughts, speech, or behavior. Common symptoms associated with psychotic disorders such as Schizophrenia include delusions, or beliefs that are unfounded or unreal, and hallucinations, which are perceptions or sensations that are unreal. While the age of Schizophrenia diagnosis is commonly reported in early adulthood, cortical thinning and other indicators of brain function have been shown to differ considerably in earlier developmental stages such as late childhood and early adolescence (Kubota et al. 2011; Whitfield-Gabrieli and Ford 2012).

Moreover, symptom dimensions have been explored as they relate to changes in the brain. Schizophrenia is characterized by both positive and negative symptoms. Positive symptoms refer to the abnormal presence of psychotic activity such as hallucinations and delusions. Negative symptoms refer to the absence of adaptive behaviors such as apathy, avolition, and anhedonia. Previous literature indicates that persons with Schizophrenia who present more negative symptoms, such as avolition and apathy, showed impaired performance on reward-related paradigms such as the MID task (Strauss et al 2014). Negative symptoms are of considerable interest because they are less effectively treated with medication, and negative symptoms show differences in brain activity across Schizophrenia, depression, substance use, and obsessive-compulsive clinical disorders (Admon & Pizzagalli 2015; Green et al. 1999; Chau et al. 2004).

Comorbid Cannabis Use and Schizophrenia

While chronic substance use has commonly been associated with attenuated or deficient reward processing and motivational impairments behaviorally (David et al. 2005), researchers have begun to examine how pharmacological interventions and extended use may impact reward circuitry in the nervous system. Cannabis provides an interesting role as it potentially facilitates reward processing among chronic users in ways that are different from other commonly used substances. Acute effects of cannabis have been observed to interact with the endocannabinoid system in the brain via cannabinoid (CB1) receptors, which are densely populated along mesolimbic and mesocortical pathways (Mauzay et al. 2021).

Chronic use of cannabis has been examined for its effects on reward processing in the brain. Nestor et al. (2010) tested the performance of chronic cannabis users, those who use more than five times a day as well as over 500 "joints" consumed overall, to non-users for a monetary incentive delay task. Participants were presented with win, loss, and no-outcome conditions paired with a valued cue of fifty cents. To assess anticipation to non-drug related cues, MID stimuli consisted of smiley or frowny faces, and the feedback included images of fifty cents. Nestor et al. found increased activity in the ventral striatum during reward anticipation compared to non-users. However, there was not a difference in behavioral performance between cannabis and non-users. Nestor and colleagues have suggested that cannabis may be increasing reward sensitivity by dopamine release in the ventral striatum.

Wotruba et al. (2014) conducted a functional connectivity analysis of reward related brain regions during a monetary incentive delay task for people at risk for psychosis and healthy controls. Activation strength in the ventral striatum was correlated with positive symptoms, and negative symptoms were associated with changes in brain activity during reward receipt.

Wotruba et al. found that individuals at risk for psychosis showed similar task accuracy compared to healthy controls. Those at risk showed increased activation in posterior cingulate cortex (PCC) , medial frontal gyrus (MFG) , and superior frontal gyrus (SFG) compared to controls, and the two groups did not differ in activation during reward receipt. However, symptom dimensions were related to differences in activation during anticipatory phases. Positive symptoms were found to correlate with increased activation in the ventral striatum. There was also an inverse correlation between negative symptoms and activation in the ventral striatum during reward receipt. The hyperactivity of frontal regions during anticipation has been suggested to relate to an increased effort required to perform the task. Moreover, the authors discuss hyperactivity of the PCC due to this region being a key area in the Default Mode Network. The study also found decreased activation in medial orbitofrontal cortex regions for at risk individuals compared to controls. These findings are consistent with other neuroimaging studies that have identified hyperactivity of Default Mode Network regions in individuals during prodromal stages of psychotic symptoms (Whitfield-Gabrieli et al. 2009). Those at risk for psychosis and persons with schizophrenia have been observed to show hyperactivity of default mode and reward network brain regions. However, it is not clear how chronic use of substances, such as cannabis, may promote changes in network connectivity and how it relates to reward learning behaviors.

Current Study Introduction

Researchers have suggested that patients may use cannabis to ameliorate challenges with reward and value processing. The present dataset has been explored to investigate interregional connectivity before and after cannabis intake for patients with comorbid cannabis use disorder (CUD) and Schizophrenia (SCZ). Fischer et al. (2014) used resting-state functional connectivity

analysis to find reduced connectivity of prefrontal regions, including the anterior prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex regions, with the nucleus accumbens for patients compared to healthy controls. These findings may suggest impaired value processing of reinforcers for patients with Schizophrenia.

While findings from Fischer and colleagues indicate implications for reward processing, task-based paradigms may provide additional insight into reward processing and learning by directly measuring participants' response to reinforcers. Moreover, connectivity recruitment of cortical regions with ventral striatal activity has been found to reflect value processing and cognitive control outcomes (Davidow et al. 2016; Gerraty et al. 2014).

The Monetary Incentive Delay (MID) task (Knutson et al. 2000) pairs a cue with a reward value, typically money, to model approach behaviors in humans and other animals. Conditions may vary based on the value of the reward as well as the inclusion of both gain and loss conditions. Previous studies have found that high values produce better behavioral performance, faster reaction time, and higher accuracy compared to low value rewards in healthy adults (Lutz and Widmer 2014; Adcock et al. 2006).

The present study will further explore the relationship between functional connectivity and behavioral measures of reward processing. Using the MID paradigm as well as resting-state functional connectivity analysis, outcomes for patients with comorbid SCZ and CUD will be compared to healthy controls to determine the impact of cannabis. The study will test whether patients with Schizophrenia show reduced accuracy or slower reaction time compared to healthy controls. Especially, how does patient performance on the MID task change before and after cannabis. Differences in brain function between groups will be assessed using functional connectivity analysis.

Materials and Methods

The present project collected behavioral responses to reward cues for patients with comorbid Schizophrenia (SCZ) and Cannabis Use Disorder (CUD) compared to healthy controls (HC). Two resting scans for all participants were collected one week apart from one another, and the reward task was completed before both scans. Patients with Schizophrenia were administered cannabis in a randomized choice of joint or THC pill before their second scan and task.

Participants

Eleven patients with comorbid SCZ and CUD and thirteen healthy control subjects participated in the study. All participants were of Caucasian ethnicity. Three SCZ participants were female, and eight were male. Four healthy control participants were female, and eight were male. One healthy control declined to report this information. The mean age for the SCZ group is 37.09 (min: 24, max: 50), and the mean age for the HC group is 33.5 (min: 21, max: 48).

Patient group participants were diagnosed with both SCZ and CUD using the Structured Clinical Interview for the Diagnostic and Statistical Manual (First et al. 1997). Patients were required to be on stable antipsychotic medications. Healthy controls were matched with SCZ patients based on age, gender, and handedness. SCZ participants with additional substance use were included, however, patients taking clozapine medication were excluded from screening (Fischer et al. 2014).

Cannabis Administration

Participants were instructed to remain abstinent from cannabis between scan one and scan two. All patients received cannabis intervention, where patients received a double-blind randomized assignment of either a THC pill or cigarette. Each patient was given both a pill and a

cigarette, and the following manipulations were assigned to each patient including THC pill or placebo pill, and THC joint or a placebo joint. Healthy controls were not administered cannabis.

Reward Response Paradigm

All participants completed a Monetary Incentive Delay (MID) task before each scanned session (Knutson et al. 2000). The MID task presented contained four conditions of differing reward values including a low reward value of thirty cents, a high reward value of three dollars, no reward value of zero dollars, and a no response condition. See Figure 1 for reward conditions. Stimuli cue consisted of a cartoon pink pig to simulate a piggy bank with coins or dollars visible for the low and high reward respectively. A crosshair target was presented after the cue and did not change by condition. Participants were instructed to respond as quickly and as accurately by pressing a button after viewing the cue. Feedback stimuli was presented that either drew an 'X' over the original cue for incorrect responses or the money from the original cue was placed inside the piggy bank to signal correct responses. Cues were presented ten times for each of the four conditions (40 cues presented total). Feedbacks for wins and losses have a requested duration of 1.65 s. Feedback comes after a varying delay of 3.1-3.6 s from the presentation of the crosshair target. While functional neuroimaging was also collected during the task, the present project investigates resting scan data for patients and healthy controls.

Brain Image Acquisition

Two sessions were conducted per participant for the resting scan and a behavioral task to take place. For all participants, the second scan was scheduled at least seven days later than the first. For patients, session one was scanned while the participant abstained from cannabis, the second session was scanned after cannabis administration. The scan lasted eight minutes. Neuroimaging data was collected using functional magnetic resonance imaging. Both sessions

were scanned using a 3T Philips Achieva fMRI scanner with an 8 channel head coil. See Fisher et al. (2014) for a detailed explanation of scan acquisition.

Behavioral Analysis

A mixed effects repeated measure ANOVA using ezANOVA package (Lawrence & Lawrence 2016) was conducted for multiple comparisons 2 groups x 3 reward conditions of accuracy for the MID task. The analysis used Mauchly's Test for Sphericity to test for violations of assumptions of ANOVA, such as unequal variances. Corrected p-values are reported based on the sphericity test. Post-hoc t-tests were conducted to examine differences in accuracy and reaction time between sessions as well as groups.

Resting State fMRI Preprocessing

The CONN toolbox for functional connectivity analysis (Whitfield-Gabrieli & Nieto-Castanon 2012) was used to preprocess the brain imaging using SPM12 scripts (Friston et al. 1991). Preprocessing steps included realignment, segmentation, normalization, as well as motion correction.

The CONN preprocessing pipeline (version 20b) normalized volumetric data to the Montreal Neurological Institute (MNI) template and corrected slice time based on interleaved image collection. The subject-motion threshold was set to 0.9 mm for correction. The sampling resolution of anatomical and functional outputs were set to the defaults of $1mm^3$ for anatomical and $2mm^3$ for functional images. The Gaussian kernel was set to the default of 8mm for smoothing of voxels.

Resting State fMRI First-Level Analysis

Eleven patients and eleven healthy controls were preprocessed for analysis (two HCs and one SCZ subject were excluded due to missing or corrupted data). A general linear model was

estimated to fit the brain data. A seed to voxel analysis was used to assess correlation of regional activation. Connectivity maps were generated based on the weighted general linear model after including regressors of confounding movement and physiological effects.

Resting State fMRI Second-Level Analysis

Whole brain seed to voxel analysis was completed for both healthy control and patient groups. Bilateral NAcc was used as a source seed to assess correlation with voxels at a threshold of $p < 0.001$. Random Field Theory parametric statistics were set to a FDR-corrected threshold of $p < 0.05$ cluster-size.

Results

Analysis of accuracy and reaction time for the MID task is reported across sessions. Functional connectivity analysis is reported for healthy control and patient groups for session one. Future analysis of this data is recommended given time limitations of this research.

Behavioral Results

In order to test the effects of reward value on accuracy and reaction time of the MID task, an analysis of variance was completed comparing the patient group to the healthy control group. ANOVAs were isolated by session to capture the effects of cannabis.

For session one, a mixed effects ANOVA revealed a significant main effect of reward condition for accuracy ($F_{2,44} = 25.52$, $p < 0.0001$). There was a main effect of group at trend level ($F_{1,22} = 3.87$, $p = 0.062$), which did not reach threshold for statistical significance. There was no significant interaction between reward condition and group on accuracy ($F_{2,44} = 0.123$, $p = 0.730$). A mixed effects ANOVA also revealed a significant main effect of reward condition for reaction time ($F_{2,44} = 3.96$, $p < 0.05$). There was no significant effect of group ($F_{1,22} = 0.52$, p =

0.48) or an interaction of group and reward condition ($F_{2,44}$ = 1.18, p = 0.317) for reaction time. Figure 4 includes total mean accuracy of patients and controls for high and low values.

For session two, there was a significant main effect of group on accuracy ($F_{1,22}$ = 7.969, p <0.001). There was also a significant main effect of reward condition on accuracy. ($F_{2,44}$ = 35.23, p <0.0001). There was no significant interaction between group and reward condition ($F_{2,44}$ = 0.354, p = 0.703). For session two, there were no significant effects of group ($F_{1,22}$ = 1.84, p = 0.189), and there was no significant interaction. There was an effect of reward condition that did not reach significance ($F_{2,44}$ = 2.904, p = 0.066). No change in effects were observed after controlling for session one reaction time.

Post-hoc related t-tests found a significant difference between session one (mean: 0.808) and session two (mean: 0.850) accuracy in healthy controls (-3.926, df = 24, p < 0.01) for the high-reward condition where session two showed higher accuracy. There was not a significant difference for high-reward accuracy between session one (mean: 0.748) and session two (mean: 0.728) for individuals with SCZ (.620, df = 19, p = 0.549. For session one, healthy controls (mean: 0.808) showed higher accuracy than patients (mean: 0.748), but this effect did not reach significance (-1.95, df = 21, p = 0.064). For session two, there was a significant difference (3.17, df = 22, p < 0.01) for high-reward accuracy between groups where healthy controls (mean: 0.850) were more accurate than patients (mean: 0.728).

There was no significant difference in high reward reaction time between session one and session two for healthy controls (-1.24, df = 24, p = 0.227, S1 mean: 0.237, S2 mean: 0.226) and SCZ individuals (0.379, df = 20, p = 0.709, S1 mean: 0.247, S2 mean: 0.243) respectively, and there were no significant differences between groups for session one (-1.125, df = 22, p = 0.273, HC mean: 0.237, SCZ mean: 0.247) nor session two for reaction time (-1.977, df = 21, p

= 0.06, HC mean: 0.226, SCZ mean: 0.243). However, the effect is at trend level for the second session where healthy controls respond faster than patients.

Resting State Brain Network

Within-group whole brain seed-to-voxel analysis using an averaged bilateral NAc source ROI and a false discovery rate (FDR) correction for multiple comparisons of $p<0.05$ revealed significant connectivity between the NAc and reward related cortical-regions in both patients and healthy controls. Both patients and healthy controls showed activation in orbitofrontal cortex, anterior cingulate gyrus, paracingulate gyrus, subcallosal cortex, and insular cortex. See Figure 1 for activation overlays. Between-group contrast of HC > SCZ of NAcc did not reach significant differences in correlated regions. Post-hoc expansion region of interest to voxel analysis of caudate, putamen, and NAcc (ventral striatum) contrasting HC > SCZ analysis of connectivity during rest revealed decreased activity in insular cortex regions for patients. These are included as multi-slice overlays in Figure 3.

Discussion

The current project observes that patients and controls respond similarly to value cues during the MID task before cannabis use, and patients are less accurate after cannabis administration. Accuracy of trials was better for the higher valued reward cues for both patient and control groups. Accuracy for incentive delay tasks has been shown to be related to the value of the reward, where more rewarding reinforcers produce higher accuracy, which is expected for healthy controls (Lutz & Widmer 2014). However, after consumption of cannabis, patients performed worse than controls. Based on these findings from the MID task, cannabis worsens accuracy. Cannabis has been shown to impair some cognitive functions with acute and chronic use, and these effects are often compounded for persons with psychotic symptoms (Kroll et al.

2020; Mauzay et al. 2021) However, these findings are based on the total accuracy of all conditions and may change if considered for accuracy of only high value rewards. Reaction time showed little difference between groups and reward conditions.

In the brain, controls and patient groups had similar functional connectivity within the Reward Network. Functional connectivity in frontal regions with nucleus accumbens was observed in both groups. Both groups showed functional connectivity in anterior cingulate cortex and orbitofrontal cortex, which are regions associated with the evaluation and outcomes of reward values (Haber 2011). The lack of group difference may not indicate attenuated connectivity for patients, which is inconsistent with previous work on the dataset. This may suggest the methods of this project did not reach data saturation, and additional analysis of samples are recommended.

Because ventral striatum connectivity as a whole may also characterize reward processing, I included putamen and caudate nucleus with nucleus accumbens for ROI-to-voxel analysis, and the insular cortex showed less functional connectivity for patient group compared to controls for this region. The insular cortex is associated with the input of sensory information during reward processing (Haber 2011), and this area should be further explored for its role in sensory and value processing.

Limitations

The present project fails to capture the effects of cannabis in the brain due to limited scope. Moreover, further research is required to untangle reward network coactivation. In order to better relate behavioral performance to reward processing and resting brain activity, a scanned MID task including trial by trial data may characterize patients' response to reward values more accurately. Functional connectivity should be assessed during the task before and after cannabis.

While previous resting state analysis has indicated reduced functional connectivity before cannabis and compared to healthy controls, comparison of resting state and task brain data will represent how changes in the brain occur while responding to reward cues. Additionally, stages of reward processing such as anticipation and receipt may be assessed comparing by patient status before and after cannabis.

Future work should also use additional paradigms to capture reward learning. The present project allows exploration of low and high value rewards; however, responses may vary based on gain or loss trials for patients or healthy controls. Moreover, probabilistic learning paradigms may also give insight into how patients integrate feedback from rewards for decision making. The effects of cannabis may be critical due to their implications of working memory and cognition broadly for both persons with Schizophrenia and healthy controls (Rabin et al. 2011).

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Tables

Table 1

Healthy Control Functional Connectivity with NAcc Results

Atlas Region	Voxels	Coverage
AC (Cingulate Gyrus, anterior division)	667 voxels (8%)	covering 26% of
PaCiG l (Paracingulate Gyrus Left)	460 voxels (5%)	covering 35% of
MedFC (Frontal Medial Cortex)	82 voxels (1%)	covering 8% of
Caudate left	383 voxels (6%)	covering 74% of
PaCiG r (Paracingulate Gyrus Right)	462 voxels (5%)	covering 34% of
Caudate right	334 voxels (5%)	covering 64% of
Putamen left	321 voxels (5%)	covering 37% of
SubCalC (Subcallosal Cortex)	533 voxels (6%)	covering 47% of
FOrb r (Frontal Orbital Cortex Right)	98 voxels (1%)	covering 7% of
FOrb l (Frontal Orbital Cortex Left)	279 voxels (3%)	covering 17% of
Putamen r	383 voxels (5%)	covering 48% of
Accumbens l	107 voxels (2%)	covering 100% of
Thalamus left	144 voxels (2%)	covering 11% of
Thalamus right	140 voxels (2%)	covering 11% of
Accumbens r	84 voxels (1%)	covering 100% of
IC l (Insular Cortex Left)	36 voxels	covering 3% of

Pallidum left	89 voxels (1%) of	covering 29% of
Pallidum right	76 voxels (1%)	covering 28% of

Table 1. Significant voxels correlated with nucleus accumbens seed are listed with percentage of region of interest covered for healthy controls. All reported values reached cluster extent threshold FDR-corrected significance of $p<0.05$.

Table 2

Patient Functional Connectivity with NAcc

Voxels	Coverage	Atlas Region
650 voxels (11%)	covering 25% of	AC (Cingulate Gyrus, anterior division)
435 voxels (7%)	covering 33% of	PaCiG l (Paracingulate Gyrus Left)
425 voxels (7%)	covering 43% of	MedFC (Frontal Medial Cortex)
387 voxels (6%)	covering 72% of	Caudate left
336 voxels (5%)	covering 25% of	PaCiG r (Paracingulate Gyrus Right)
334 voxels (5%)	covering 64% of	Caudate right
321 voxels (5%)	covering 37% of	Putamen left
309 voxels (5%)	covering 27% of	SubCalC (Subcallosal Cortex)
121 voxels (2%)	covering 8% of	FOrb r (Frontal Orbital Cortex Right)
121 voxels (2%)	covering 7% of	FOrb l (Frontal Orbital Cortex Left)
116 voxels (2%)	covering 14% of	Putamen r
107 voxels (2%)	covering 100% of	Accumbens l
104 voxels (2%)	covering 23% of	aMTG l (Middle Temporal Gyrus, anterior division Left)
86 voxels (1%)	covering 1% of	FP r (Frontal Pole Right)
84 voxels (1%)	covering 100% of	Accumbens r

82 voxels (1%)	covering 6% of	IC l (Insular Cortex Left)
76 voxels (1%) of	covering 25% of	Pallidum l
64 voxels (1%)	covering 1% of	FP l (Frontal Pole Left)
46 voxels (1%)	covering 3% of	pMTG l (Middle Temporal Gyrus, posterior division Left)
39 voxels (1%)	covering 2% of	TP l (Temporal Pole Left)

Table 2. Significant voxels with nucleus accumbens seed are listed with percentage of region of interest covered for patients. All reported values reached cluster extent threshold FDR-corrected significance of $p<0.05$.

Figures

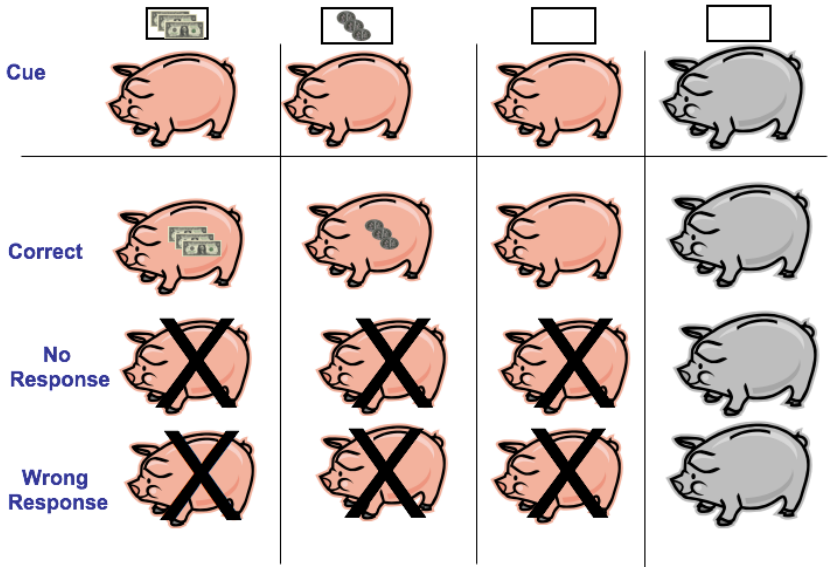

Figure 1. Monetary Incentive Delay task stimuli depict the four cues: high value of three dollars, low value of thirty cents, no reward value, and no response conditions.

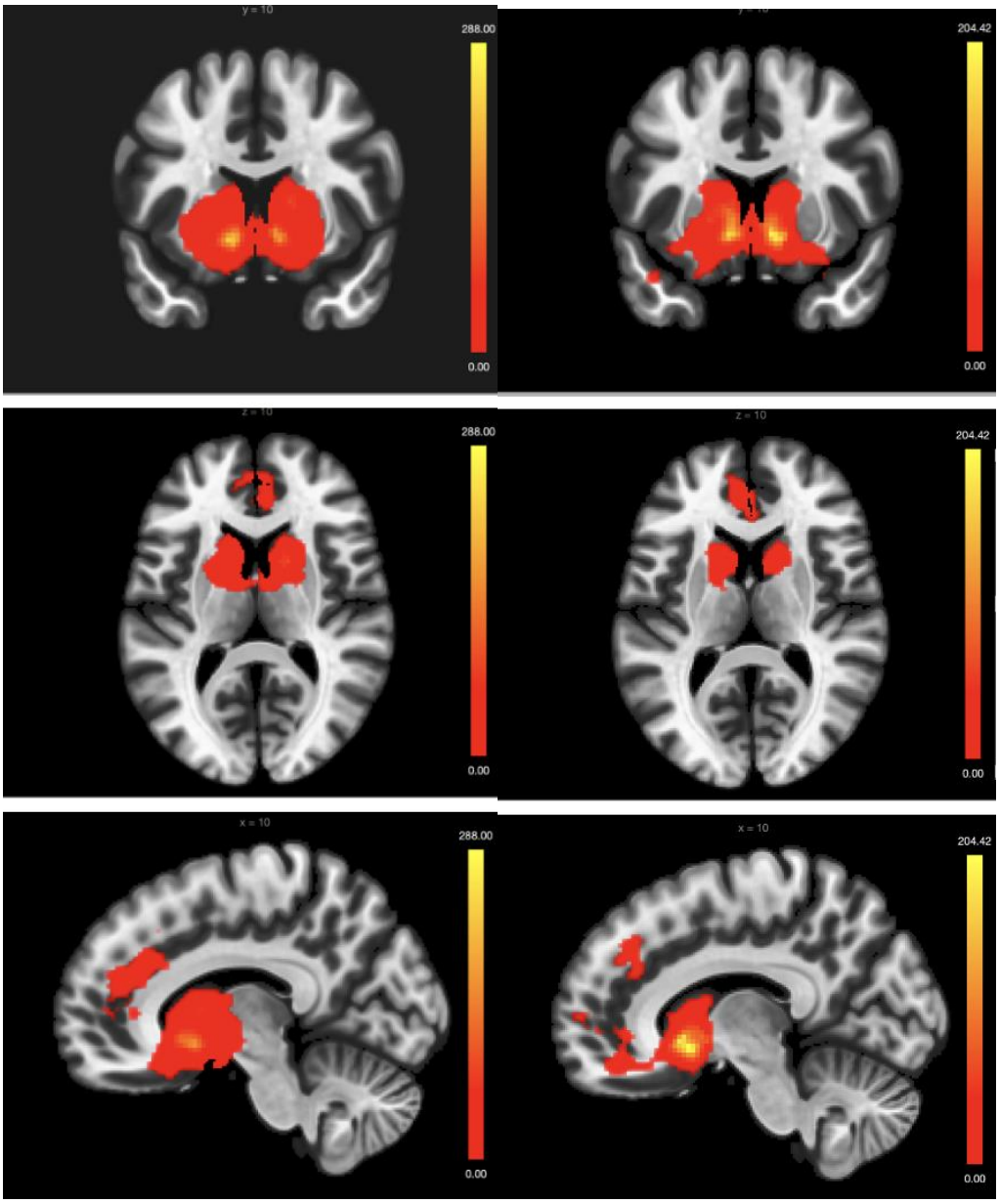

Figure 2. HC (left) and SCZ (right) show NAcc correlated voxels for coronal, axial, and sagittal slices located at (10,10,10) coordinates.

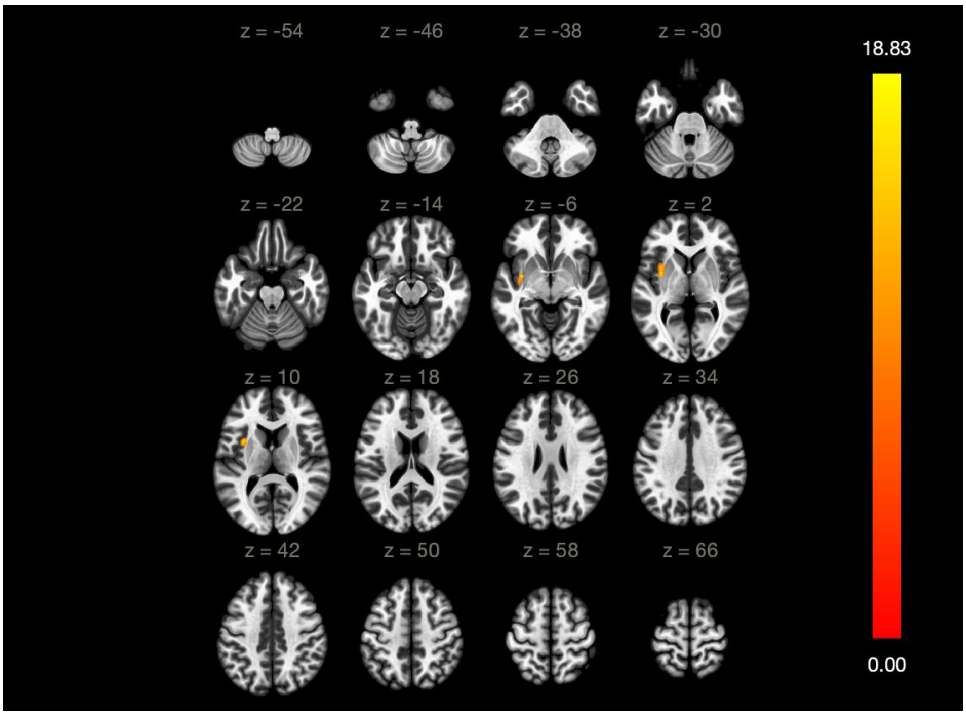

Figure 3. Multi-slice view of HC > SCZ contrast of correlated voxels with ventral striatum including bilateral putamen, caudate, and nucleus accumbens.

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Figure 4. Histograms displays total mean accuracy by high and low conditions for patients and controls.