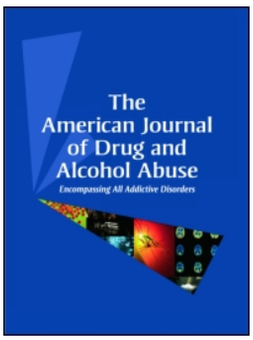

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ORIGINAL ARTICLE

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Striatal functional connectivity in chronic ketamine users: a pilot study

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ABSTRACT

Background: The striatum supports motivated behavior and impulse control. Altered striatal activation and connectivity has been observed in link with impulse control dysfunction in individuals with drug addiction.

Objectives: We examined how resting state functional connectivity (rsFC) of the striatum is altered as a result of chronic ketamine misuse.

Methods: Thirty-six ketamine users (10 women) and 20 healthy controls (9 women) completed an assessment with the Barratt Impulsiveness Scale (BIS-11) and magnetic resonance imaging. In SPM we examined voxel-wise connectivities of the caudate, pallidum, putamen, and ventral striatum in ketamine users (versus healthy controls) and in association with BIS-11 score and duration of use, all at a corrected threshold.

Results: Compared to controls, ketamine users showed higher connectivity between caudate and dorsal anterior cingulate cortex and between pallidum and bilateral cerebellum. In ketamine users, putamen showed higher connectivity with the left orbitofrontal cortex (OFC) in association with both BIS-11 score and months of ketamine use. Mediation analyses suggest that the connectivity z score mediated the relationship between impulsivity and duration of use.

Conclusions: These preliminary findings highlighted altered striatal connectivity in chronic ketamine users, and the potential role of putamen OFC connectivity in supporting the correlation between impulsivity and duration of ketamine use. If replicated in a larger sample, these findings may represent neural markers of ketamine misuse.

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Ketamine; SUD; impulsivity; fMRI; striatum; insula; sex difference

Introduction

Impulsivity, striatum, and addiction

Though not listed as a diagnostic criterion in DSM-5, impulsivity is one of the core characteristics of substance use disorders (SUD). Many studies have pointed out the pivotal role of impulsivity in the initiation and maintenance of drug seeking and consumption (1–6). Impulsivity along with sensation seeking prompted first use of illicit substances in adolescents (7,8). Patients with opioid or cocaine dependence showed higher impulsivity as assessed with the Barratt Impulsivity Scale (BIS-11) (9–12), Eysenck's I7 Impulsiveness Inventory (13) or delayed discounting tasks (14). Higher impulsivity was associated with more risky behaviors (15,16), and worse prognosis (17,18) in individuals with SUD, and impulse control represents an important target in the treatment of SUD.

The striatum is a critical component of the reward circuit. It has been linked to the drive for immediate reward gratification with robust response during anticipation of monetary reward and reinforcement learning (19). As individuals progress from occasional to compulsive drug use, drug-seeking behavior shifts from being reward to habit driven (20), and the dorsal striatum becomes increasingly involved during this transition (21,22). Selective lesions of the nucleus accumbens core induced persistent impulsive choice in rats (23). Lesion studies in animals showed distinct roles of the lateral and medial dorsal striatum in response selection and inhibition (24). In functional imaging of humans, striatal activation tends to accompany impulsive responding (25). An earlier study showed that intrinsic network connectivity of the striatum was significantly weaker in cocaine users relative to controls, in relation to greater non-planning

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impulsivity in cocaine users (26). In another study, cocaine-addicted individuals exhibited reduced connectivity between the putamen and posterior insula and right postcentral gyrus, and the reduction in connectivity partially mediated Barratt impulsivity in cocaine-addicted participants (27). Together, a substantial body of evidence suggests that the fronto-striatal circuitry balances impulsive and controlled decision-making (28), and fronto-striatal circuit dysfunction is associated with impulsive behavior (28) and trait impulsivity in individuals with SUD (29,30).

Functions of striatum

The striatum comprised a number of nuclei with distinct anatomical connections and functions (31,32). Anatomically, the cerebral cortex projects widely to the striatum with a topographical organization. The caudate nucleus receives inputs primarily from the medial and lateral prefrontal cortex and both the putamen and pallidum receives inputs from the motor cortex. Striatal output nuclei project to the thalamus, which sends projections back to the cerebral cortex, forming a cortical-striatal-thalamic-cortical circuit for motor and cognitive control. This circuit parallels the cortical-pontine-cerebellar-thalamic-cortical loop and supports large-scale integration of motor and "higher" cognitive functions (33). Dysfunction of these circuits have been implicated in the etiology of many neuropsychiatric conditions (34–36).

Numerous studies have characterized the roles of the striatum in motor and cognitive control and in reward processing (31,32,37). As these processes are all intricately related to impulsivity, we explored the relationship between the functional connectivity of the basal ganglia in relation to individual impulsivity as assessed by the Barratt Impulsivity Scale. Further, cortical projections to the striatum are largely glutamatergic and chronic use of ketamine, an antagonist of N-Methyl-D-aspartate (NMDA) receptor, may influence functional connectivity of the basal ganglia.

Ketamine abuse in Asia

Besides amphetamine-type stimulants, many new psychoactive drugs sneak up in the abused drug scenes involving Asian youth. Among them, ketamine has become one of the major substances of abuse. In Hong Kong, ketamine has been the most common substance of abuse in teenagers since 2005 (38) and ketamine-related events accounted for 7.1% of all toxicology consultation in the year 2010 (39). In Taiwan, in a National Household Survey on health and substance abuse conducted in 2005 by the Department of Health and Welfare, ketamine ranked third (22%), following amphetamine (49%) and MDMA (35%), as the most used illicit substance in the population 12 to 64 years of age. Among high school students who used club drugs, 64.4% reported using ketamine, followed by ecstasy (50%) and methamphetamine (29%). The average age at first ketamine use was 13.95 years, a critical period of adolescent brain development.

Importantly, whereas ketamine is frequently used concomitantly with other illicit drugs in western countries (40–45), use of ketamine as the primary or sole substance is not rare in Asia (46,47). This has created a tremendous public health issue but also provided a unique opportunity to study the long-term consequences of chronic ketamine exposure.

The current study

Despite grave concerns for growing ketamine use, there have been few studies of the neuropsychological consequences of chronic ketamine exposure. Even fewer studies have directly employed brain imaging to investigate neural dysfunction in chronic ketamine users. Ketamine affects NMDA receptor system and has powerful effects on many cognitive functions including impulse control. Ketamine or NMDA antagonists treatment increased impulsive choice dose-dependently in animal models (48–51) and impulsivity in humans (52,53), suggesting that ketamine exposure may contribute to diminished inhibitory control. Importantly, the striatum receives glutamatergic inputs from the prefrontal cortex to support learning and goal-directed behavior (54), and dysfunction of these processes is intricately related to drug addiction (55). Here, we examined resting state functional connectivity (rsFC) of the striatum as a neural metric to investigate how ketamine may alter cerebral circuit functions. Specifically, we contrasted a group of chronic ketamine users with demographically matched non-drug using controls in striatum rsFC. We will explore group differences in trait impulsivity and the neural bases of impulsivity in ketamine users as well as the influences of the duration of ketamine use on striatal connectivity. We would like to note that the current study was not powered to examine sex differences and thus men and women were combined in data analyses.

Experimental procedures

Subjects and clinical assessments

The Research Ethics Committee of the China Medical University Hospital approved the study protocol (CMUH103-REC2-052). Candidates were assured at

screening that their decision to participate in the study or not would not affect their right to medical care, that all personal information would be kept confidential, and that they could withdraw from the study at any time. Each participant provided a written informed consent prior to data collection.

Ketamine-using and healthy control participants were recruited through posters at hospitals and online advertisements in the greater area of Taichung City, Taiwan. After consenting to the study, participants completed a clinical interview, questionnaire assessment, behavioral test, and magnetic resonance imaging. Ketamine users met the International Statistical Classification of Diseases and Related Health Problems (ICD) criteria for ketamine use disorders and tested positive for ketamine in urine toxicology. A positive test result for other substances including methamphetamine, opioids, ecstasy, or marijuana, was an exclusion criterion. All healthy control participants denied the use of any illicit substances and showed negative urine test results. None of the ketamine using or healthy control participants had any major medical or neurological illnesses, history of brain concussion that resulted in the loss of consciousness or psychotic disorders. A total of 36 ketamine users and 20 healthy controls participated in this study. Table 1 summarizes the key clinical characteristics of the participants.

Magnetic resonance imaging: procedures and parameters

Participants underwent an MRI scan, consisting of 10 min resting-state fMRI (with eyes closed) and high-resolution structural imaging. MR image data were acquired using a 3-Tesla scanner (Signa HDx, GE, Milwaukee, USA) at the Department of Radiology, China Medical University Hospital, Taichung, Taiwan. The high-resolution structural images were acquired in transverse plane along the AC-PC line. A three-dimensional spoiled gradient-recalled protocol with inversion recovery pulse prepared (3D-SPGR-IrP) sequence was used (parameters: TE = 2.98 ms; prep time = 450 ms; flip angle = 12 degree; image matrix = 224 × 224; FOV = 224 mm × 224 mm; slice thickness = 1 mm; NEX = 1). The resting-state fMRI data were acquired using a gradient echo single-shot echo planar imaging sequence (parameters: TE = 35 ms; TR = 2000 ms; slice thickness = 4.4 mm; slice number = 32; image matrix = 64 × 64; FOV = 240 mm; total scan time = 10 min). Four dummy scans acquired at the beginning of EPI were discarded.

Imaging data pre-processing

Brain imaging data were preprocessed using Statistical Parametric Mapping (SPM 12, Wellcome Department of Imaging Neuroscience, University College London, U.K.). We followed standard procedures in image preprocessing, as in recent work (56–60). Images of each individual subject were first realigned (motion corrected) and corrected for slice timing. A mean functional image volume was constructed for each subject per run from the realigned image volumes. These mean images were co-registered with the high-resolution structural image and then segmented for normalization with affine registration followed by nonlinear transformation (61,62). The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each subject. Finally, the images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum.

Additional preprocessing was applied to reduce spurious BOLD variances that were unlikely to reflect neuronal activity (63–66). The sources of spurious variance were removed through linear regression by including the signal from the ventricular system, white matter, and whole brain, in addition to the six parameters obtained by rigid body head motion correction. First-order derivatives of the whole brain, ventricular and white matter signals were also included in the regression.

Cordes and colleagues suggested that BOLD fluctuations below a frequency of 0.1 Hz contribute to regionally specific BOLD correlations (67). Thus, we applied a temporal band-pass filter ($0.009 < f < 0.08$ Hz) to the time course in order to obtain low-frequency fluctuations, as in previous studies (64–66,68). As extensively

Table 1. Clinical characteristics of the participants.

	KU (M) n = 26	KU (W) n = 10	HC (M) n = 11	HC (W) n = 9	group effect *p* value
Age (years)	25.2 ± 5.8	27.5 ± 5.7	25.3 ± 4.5	25.1 ± 4.2	0.45
BIS-11 score	55.5 ± 7.1	60.0 ± 11.0	53.0 ± 7.4	48.6 ± 3.5	0.003
Ketamine use duration* (months)	59.4 ± 37.0	59.0 ± 40.0	NA	NA	NA
Cigarette in 30 days (days)	24.5 ± 11.1	30.0 ± 0.0	1.5 ± 2.5	0.0 ± 0.0	3.6×10^{-16}
Cigarette in life (years)	8.4 ± 4.7	12.1 ± 7.7	2.5 ± 3.5	0.0 ± 0.0	4.2×10^{-8}
Alcohol in 30 days (days)	4.8 ± 8.5	9.0 ± 11.1	3.0 ± 3.8	0.4 ± 0.7	0.02
Alcohol in life (years)	4.3 ± 4.3	6.7 ± 6.2	5.2 ± 6.2	1.9 ± 3.4	0.18

All values are mean ± SD; KU: ketamine users; HC: healthy controls; BIS-11: Barratt Impulsivity Scale; M: men; W: women; All *p* values were obtained from ANOVA except for ketamine use duration (*), where KU men and women were compared with a two sample t-test.

investigated in Van Dijk et al., 2012, micro head motion (> 0.1 mm) is an important source of spurious correlations in rsFC analysis (69). Therefore, we applied a "scrubbing" method proposed by Power and colleagues (70) and successfully applied in previous studies (70–72) to remove time points affected by head motions. Briefly, for every time point t, we computed the framewise displacement given by $FD(t) = |\Delta d_x(t)| + |\Delta d_y(t)| + |\Delta d_z(t)| + r|\alpha(t)| + r|\beta(t)| + r|\gamma(t)|$, where $(d_x, d_y, d_z)$and (α, β, γ) are the translational and rotational movements, respectively, and r (= 50 mm) is a constant that approximates the mean distance between the center of MNI space and the cortex and transform rotations into displacements (70). The second head movement metric was the root mean square variance (DVARS) of the differences in % BOLD intensity I(t) between consecutive time points across brain voxels, computed as follows: $DVARS(t) = \sqrt{|I(t) - I(t-1)|^2}$, where the brackets indicate the mean across brain voxels. Finally, to compute each subject's correlation map, we removed every time point that exceeded the head motion limit FD (t) > 0.5 mm or DVARS(t) > 0.5% (70,72). On average, 1% of the time points were removed across subjects.

Seed-based correlation and group analyses

The caudate, putamen, and pallidum masks were obtained from the Automated Anatomical Labeling or AAL atlas (73). The ventral striatum mask is not available from the AAL atlas. Thus, as with our previous studies (74,75), we used a VS mask based on cytoarchitectonic and topographical criteria (76). All masks were in the Montreal Neurological Institute space (Figure 1).

The BOLD time courses were averaged spatially across voxels over each striatum seed. For individual subjects, we computed the correlation coefficient between the averaged time course of a seed region and the time courses of all other brain voxels. To assess and compare rsFC, we converted these image maps, which were not normally distributed, to z score maps by Fisher's z transform (77,78): $z = 0.5\log_e[(1 + r)/(1 - r)]$. The Z maps were used in group, random effect analyses. We performed a covariance analysis to compare ketamine users and healthy controls with sex as a covariate. In additional models, we also included variables of nicotine and alcohol use as covariates. All results were examined with a combination of voxel $p < .001$ uncorrected and cluster $p < .05$, FWE corrected, on the basis of Gaussian random field theory, in SPM, following current reporting standards (79).

Next, we performed whole-brain simple regression analyses each with BIS-11 score and duration of ketamine use (months) as a regressor for ketamine users, both with sex and age as covariates. For brain regions that showed a significant correlation with both duration of use and BIS-11 score in linear regressions, we derived the connectivity z scores of the regions of interest for individual subjects and followed up with mediation analyses to examine the inter-relationship between BIS-11 score, duration of ketamine use, and functional connectivity.

Mediation analyses

Across ketamine-using participants, the BIS-11 score was positively correlated with duration of ketamine use (months). Further, the putamen showed higher connectivity with the left orbitofrontal cortex (OFC) both in association with BIS-11 score and months of ketamine use (see Results). Thus, we examined in mediation analyses the inter-relationships of impulsivity, connectivity

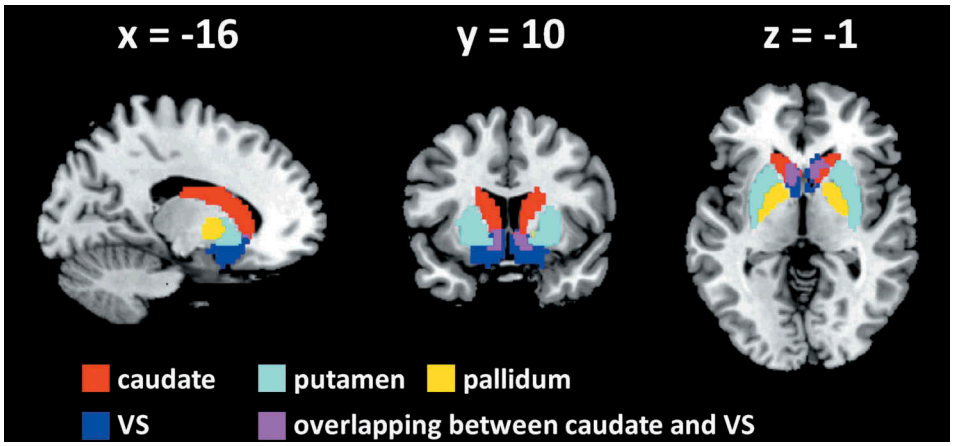

Figure 1. Seed regions: voxels overlapping between the caudate and ventral striatum (VS) were removed from each mask.

z score, and duration of use with sex and age as covariates. We performed mediation analyses (80), using the toolbox M3, developed by Tor Wager and Martin A. Lindquist (http://wagerlab. colorado.edu/tools).

In a mediation analysis, the relation between the independent variable X and dependent variable Y, i.e. X→Y, is tested to see if it is significantly mediated by a variable M. The mediation test is performed by employing three regression equations (80):

$$Y = i_1 + cX + e_1$$

$$Y = i_2 + c'X + bM + e_2$$

$$M = i_3 + aX + e_3$$

where *a* represents X→M, *b* represents M→Y (controlling for X), *c*' represents X→Y (controlling for M), and *c* represents X→Y. The constants i_1, i_2, i_3 are the intercepts, and e_1, e_2, e_3 are the residual errors. In the literature, *a, b, c* and *c*' were referred to as path coefficients or simply paths (80,81), and we followed this notation. Variable M is said to be a mediator of the correlation X→Y if (*c* – *c*'), which is mathematically equivalent to the product of the paths *a*b*, is significantly different from zero (80). If the product *a*b* and the paths *a* and *b* are significant, one concludes that X→Y is mediated by M. In addition, if path *c*' is not significant, there is no direct connection from X to Y and X→Y is completely mediated by M. Note that path *b* is the relation between Y and M, controlling for X, and should not be confused with the correlation coefficient between Y and M.

We considered and presented the results of all six models, although the primary goal was to test whether putamen OFC connectivity mediated the influence of impulsivity on the duration of ketamine use.

Results

Clinical assessments

For all clinical measures, we conducted a covariance analysis to compare ketamine users and healthy controls with sex as a covariate (Table 1). Compared to healthy controls, ketamine users showed higher BIS-11 score (p = .003). Ketamine users also showed significantly higher cigarette and alcohol use than healthy controls. Further, linear regression with sex and age as covariates showed that BIS-11 score was correlated with duration of ketamine use (months) (r = 0.34, p = .0478).

Resting-state functional connectivity (RSFC): ketamine users vs. healthy controls

In a covariance analysis of the z maps, we compared ketamine users and healthy controls with sex and age as covariates. We evaluated the results at a threshold of uncorrected voxel $p < .001$ in combination with cluster $p < .05$, FWE corrected. For the caudate nucleus, ketamine users showed higher caudate connectivity with the dorsal anterior cingulate cortex (dACC; voxel Z = 4.24, x = −9, y = 26, z = 31, 18,009 mm^3), as compared to healthy controls. (Figure 2(a)). For the pallidum, ketamine users showed greater connectivity with bilateral cerebellum (two clusters; voxel Z = 5.28, x = 27, y = −61, z = −23, 6,804 mm^3; voxel Z = 4.87, x = −30, y = −61, z = −20, 5,751 mm^3) than healthy controls (Figure 2(b)). For the putamen or ventral striatum, there were no significant group differences.

Ketamine users and healthy controls differed in the extent of cigarette and alcohol use (Table 1). Thus, we examined whether the findings described above were related to cigarette and alcohol use. We cross-correlated the z score of caudate dACC connectivity and pallidum cerebellum connectivity with years of smoking, days of smoking in the prior month, years of drinking, and days of drinking in the prior month across participants each for ketamine users and healthy controls. None of the regressions yielded significant correlations.

Impulsivity, duration of ketamine use, and striatal RSFC

We examined the rsFC of each seed region in relation to BIS-11 score and duration of ketamine use (months) for ketamine-using participants, both with sex and age as covariates. The results are summarized in Table 2. Briefly, putamen showed higher connectivity with the left orbitofrontal cortex (OFC, Figure 3(a)) and the ventral striatum (VS) showed less connectivity with the right superior temporal sulcus (STS) and left superior frontal gyrus (SFG) with higher BIS-11 score. The caudate nucleus showed higher connectivity with the cerebellum, the pallidum showed higher connectivity with the VS and ventromedial prefrontal cortex (vmPFC), and the putamen showed higher connectivity with the left OFC (Figure 3 (a)) and vmPFC, all with longer duration of ketamine use.

Mediation analyses: BIS-11 score, duration of ketamine use, putamen-OFC connectivity

The results of mediation analyses showed that putamen-OFC connectivity z score mediated the correlation bidirectionally between BIS-11 score and months of

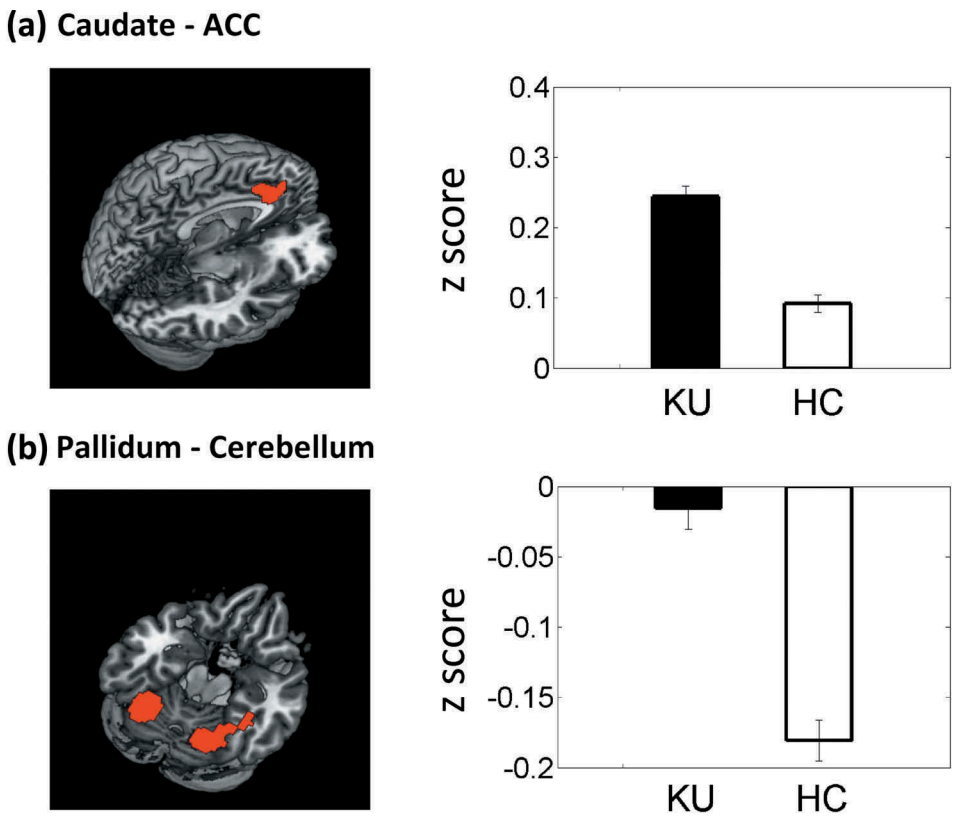

Figure 2. Examined at a threshold of $p < .001$ uncorrected, combined with cluster $p < .05$, FWE corrected, the results of whole-brain covariance analysis showed higher (a) connectivity of the caudate with anterior cingulate cortex (ACC) and (b) pallidum connectivity with the cerebellum in ketamine users (KU), as compared to healthy controls (HC). Histograms plot the mean ± S.E. of the connectivity z score of each group.

Table 2. Regions showing functional connectivity with the seed regions in correlation with impulsivity and duration of ketamine use.

	Seed region			
Regressor of interest	Caudate	Pallidum	Putamen	VS
BIS-11 score	–	–	+L OFC[1]	- R STS[2] - L SFG[3]
Duration of use (months)	+Cerebellum[4]	+VS[5] +vmPFC[6]	+L OFC[7] +vmPFC[8]	–

Note: voxel $p < 0.005$ uncorrected and cluster-level $p < 0.05$, FWE corrected; L: left; R: right; OFC: orbitofrontal cortex; STS: superior temporal sulcus; SFG: superior frontal gyrus; VS: ventral striatum; vmPFC: ventromedial prefrontal cortex. + and – each indicates positive and negative correlation with the regressor of interest. – indicates no significant findings.

1. L OFC: voxel Z = 3.47, x = −24, y = 20, z = −23, 4,023 mm^3
2. R STS: voxel Z = 3.91, x = 54, y = −64, z = 19, 6,669 mm^3
3. L SFG: voxel Z = 4.00, x = −27, y = 23, z = 49, 5,130 mm^3
4. Cerebellum; voxel Z = 3.89, x = −6, y = −55, z = −11, 6,615 mm^3
5. VS: two clusters; voxel Z = 4.69, x = 12, y = 2, z = −11, 2,241 mm^3; voxel Z = 3.59, x = −12, y = −1, z = −8, 1,836 mm^3
6. vmPFC: voxel Z = 3.64, x = 0, y = 41, z = −11, 4,833 mm^3
7. L OFC: voxel Z = 4.57, x = −33, y = 20, z = −23, 7,533 mm^3
8. vmPFC: voxel Z = 3.39, x = 0, y = 41, z = −14, 1,863 mm^3

ketamine use (Figure 3(b, c)). All other models were not significant in the mediation effect. Table 3 summarizes the statistics of all six models. Considering these findings, we also tested whether putamen-OFC connectivity was correlated with BIS-11 score in HC participants. The results of linear regression showed that the putamen-OFC connectivity z score was not correlated with the BIS-score in HC (p = .41, r = 0.19). However, the slopes did not differ significantly between the CD and HC in a slope test (p = .20, t = 1.30 (82)).

Discussion

Chronic ketamine users showed higher impulsivity than non-drug using healthy controls, as assessed by the Barratt Impulsivity Scale (BIS-11), and higher BIS score was associated with longer duration of ketamine use in ketamine users. In resting state fMRI, compared to healthy controls, ketamine users demonstrated higher caudate connectivity with the dorsal anterior cingulate cortex (dACC) and pallidum connectivity with the cerebellum. Further, in ketamine-using participants, striatal rsFC was altered in relation to both BIS-11 score and duration of ketamine use. These findings are discussed in the below.

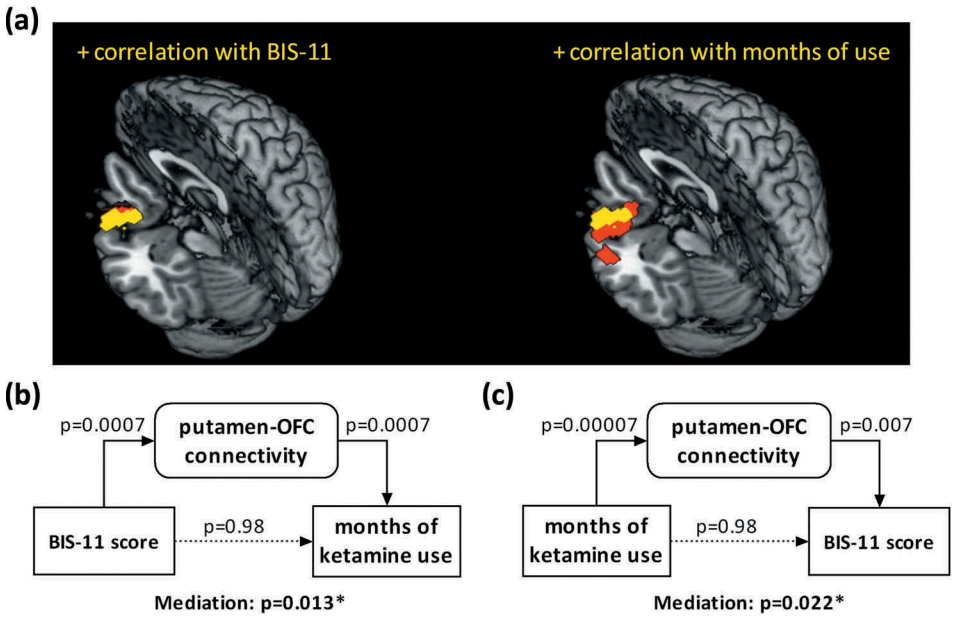

Figure 3. Putamen connectivity with the left lateral orbitofrontal cortex (OFC) was correlated positively with both impulsivity (left) and duration of ketamine use (right). (a) Voxels shown in yellow represent those that overlap between the two regressions. (b) and (c) show the results of significant mediation of the relationship of BIS-11 score and months of ketamine use, bidirectionally, by the connectivity of the overlapping voxels.

Table 3. Mediation analyses of impulsivity, duration of use, and putamen-left orbitofrontal cortical connectivity.

			p value				
X	M	Y	X → M	M → Y	X → Y	unmediated X → Y	mediated X → Y
BIS score	conn z	mo of use	0.0007	0.0007	0.047	0.98	0.013*
mo of use	conn z	BIS score	0.00007	0.007	0.047	0.98	0.022*
conn z	BIS score	mo of use	0.0007	0.98	0.00007	0.0007	0.99
mo of use	BIS score	conn z	0.047	0.007	0.00007	0.0007	0.10
BIS score	mo of use	conn z	0.047	0.0007	0.0007	0.007	0.08
conn z	mo of use	BIS score	0.0007	0.98	0.00007	0.0007	0.98

Note: conn z: connectivity z score; mo of use: months of ketamine use. *p < 0.05

Ketamine users vs. controls: caudate – dACC connectivity

Involved in reward-driven behavior (83) and in habit formation (21), the dorsal striatum is widely implicated in drug craving (84–86) and seeking (87–89). The dACC plays a role maintaining working memory, monitoring error, and processing conflict (90), and represents a core region of the saliency circuit (91,92).

Although many studies implicated the caudate and dACC, few have addressed the role of caudate dACC connectivity in the psychological processes related to drug use. Increased rsFC between dACC and caudate were reported in patients with obsessive-compulsive disorder, in positive correlation with symptom severity (93). In a treatment study of individuals with nicotine use disorders, higher functional connectivity between the caudate and dACC significantly predicted worse treatment outcome (94). In a study of neurotypical populations, individuals with less reward dependency as a personality trait rated salient visual stimuli less salient and demonstrated higher caudate dACC connectivity during expectancy of salient stimuli (95). As lower reward dependency reflects psychological distancing from the behavioral outcome, increased caudate dACC connectivity may conduce to non-goal directed or habit-like behavior, as with substance misuse. Thus, higher caudate dACC connectivity may be associated with a compromised capacity in discriminating salient stimuli for goal-directed behavior, and, as a result, compulsive drug use in ketamine users.

Ketamine users vs. controls: pallidal cerebellum connectivity

We also observed greater connectivity between the pallidum and bilateral cerebellum in ketamine users. The

cerebellum and basal ganglia are disynaptically interconnected and involved in motor and non-motor functions (see (96) for a review). The cerebellum and pallidum coactivated during appetitive conditioning with a pleasant taste stimulus in healthy subjects (97), suggesting a potential role of pallido-cerebellar connectivity in mediating reward-related processes. The cerebellum responds to reinforcement learning (98), drug cues (99), memory (100) and craving (101). Drug-induced activity-dependent synaptic changes in the cerebellum may be crucial to the transition from recreational to compulsive drug use (see (102) for a review). In other imaging studies, Koehler et al. demonstrated increased rsFC between right striatum and cerebellum in pathological gamblers (103). The findings of increased pallido-cerebellar connectivity may reflect an outcome of drug conditioning in chronic ketamine users.

Striatal connectivity in relation to impulsivity and duration of use

Barratt impulsivity and duration of ketamine use were both associated with increased putamen connectivity with the orbitofrontal cortex (OFC). Mediation analyses showed that the connectivity mediated the relationship, bidirectionally, between impulsivity and duration of use. Other models of mediation were not significant. The results suggested mutual influences between impulsivity and duration of ketamine use via cerebral connectivity. That is, impulsive personality trait may contribute to longer duration of ketamine use via increases in putamen OFC connectivity. It is statistically equally plausible that longer duration of ketamine use may render individuals more impulsive via the changes in connectivity, although Barratt impulsivity has largely been considered as a trait measure and less amenable to environmental influences.

Although no studies to our knowledge have reported alterations of putamen OFC connectivity in individuals with substance use disorders, the roles of both putamen and OFC have been examined in relation to addiction-related behavioral processes. In recordings from behaving primates, both OFC and putamen showed neuronal activities that depended upon the choice of which reward to collect in a spatial-delayed task (104). Both putamen and OFC connectivity have been implicated in self-control during delayed gratification (105). An fMRI study demonstrated a correlation between a fun seeking trait and resting-state connectivity between the OFC and putamen (106). In cigarette smokers engaged in cue reactivity tests, the putamen and OFC showed cue responses each in relation to attentional bias and craving (107). An earlier positron emission tomography study demonstrated a lower level of dopamine D2 receptor availability in the striatum, including the putamen, in association with altered metabolic rate in the OFC in stimulant abusers (108). More broadly, in rodent models, a high level of serotonin in the OFC combined with a low level of dopamine in the putamen predicted the emergence of rigid decision-making (109), a behavior reminiscent of habitual drug taking. Although mediation analyses did not distinguish the directional relationship between impulsivity and duration of use, the current findings add to the literature of putamen and OFC dysfunction in substance misuse.

Limitations of the study and conclusions

A number of limitations are worth considering. First, the sample size is small in this pilot study. In particular, a group of non-substance-abusing individuals with a wider range of impulsivity is needed to confirm whether the current findings are specific to chronic ketamine users or relate more broadly to impulsivity. In particular, the study was not powered to examine sex differences. Thus, these findings are preliminary and will need to be replicated in future work. An additional issue concerns the potential influence of psychiatric comorbidities on the current findings. We did not screen for psychiatric illnesses other than psychosis in the current study. Second, although regression analyses largely ruled out an effect of alcohol and cigarette use on the current findings, it remained unclear how these comorbidities may influence striatal connectivity. That is, while the analyses did not reveal much relationship between imaging findings and smoking/drinking variables, we could not conclude that these findings are specific to ketamine misuse. Third, questionnaires, such as the urgency, premeditation, perseverance, sensation seeking, and positive urgency (UPPS-*P*) behavioral scale (110), and behavioral tests, such as the stop signal task (111,112), may address impulsivity features not captured by the BIS-11 and reveal other changes in striatal rsFC in ketamine users. Finally, we targeted the striatum in the current study, but other regions of the frontal-limbic circuit need to be investigated in relation to impulsivity (113).

In conclusion, we demonstrated changes in resting state striatal connectivity in chronic ketamine users. Increased caudate connectivity with the anterior cingulate cortex may be related to heightened saliency response to drug cues and habitual drug seeking. Putamen connectivity with orbitofrontal cortex supported the interrelationship between impulsivity and duration of use. If corroborated in a larger sample, these findings may add to

a growing literature of the addiction neuroscience of ketamine misuse.

Disclosure statement

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