
Abnormal brain networks in stimulant use disorder.

Liam J. Nestor* and Karen D. Ersche1,2,3*

1Department of Psychiatry, University of Cambridge, United Kingdom
2Department of Systems Neuroscience, University Medical Centre Hamburg Eppendorf, Germany
3Department of Addictive Behaviour and Addiction Medicine, Central Institute of Mental Health, University of Heidelberg, Germany

*Corresponding authors
Department of Psychiatry,
University of Cambridge,
Herchel Smith Building for Brain & Mind Sciences,
Cambridge Biomedical Campus,
Robinson Way,
Cambridge CB2 0SZ,
United Kingdom
Email: ln282@cam.ac.uk and ke220@cam.ac.uk
Abstract

**BACKGROUND:** Drug addiction is associated with blunted neural responses to non-drug rewards, such as money, but heightened responses to drug cues that predict drug-reward outcomes. This dissociation underscores the role of incentive context in the attribution of “motivational salience”, that may reflect a “narrowing” towards drug-related goals. This hypothesis, however, has scarcely been investigated. **METHODS:** To address this important scientific gap, the current study performed an empirical assessment of differences in salience attribution by comparing patients with stimulant use disorder (SUD: n=41), with control (CON; n=48) participants on network connectivity related to anticipation and outcome processing using a modified monetary and drug incentive delay task. We hypothesised increased activation and connectivity to drug rewards in SUD patients, and reduced activation and connectivity to monetary rewards during incentive processing across brain networks. **RESULTS:** In the presence of behavioural and regional activation similarities, we found that SUD patients demonstrated significantly less connectivity involving three separate distributed networks during monetary reward anticipation, and drug and monetary reward outcome processing. No group connectivity differences for drug reward anticipation were identified. Additional graph theory analyses revealed that SUD patients had longer path lengths across these networks, which were all positively correlated with the duration of stimulant drug use. **CONCLUSIONS:** Specific disruptions in connectivity in networks related to the anticipation of non-drug reward together with more general dysconnectivity in the processing of rewarding outcomes suggest an insensitivity to consequences. These observations support the notion of predominance of habitual control in SUD patients.
Introduction

Stimulant drug addiction is a growing public health problem that leads to major economic and health burdens, which is difficult to treat\(^1\). Identifying and understanding disturbance across neural systems in stimulant addiction may help in the development of effective treatments\(^2\). While the initial reinforcing effects of stimulant drugs are mediated by enhanced neurotransmission in the mesolimbic dopaminergic system, the transition from recreational stimulant drug use to stimulant drug addiction is thought to progressively engage different striatal subsystems through neuroadaptations of ventromedial and dorsolateral prefrontal inputs\(^3, 4\). These neuroadaptations may account for maladaptive behaviours typically seen in stimulant-addicted individuals because they affect the interplay between two regulatory brain systems that are critical for control over behaviour: the incentive-driven goal-directed and the stimulus-bound habit systems.

The goal-directed system, subserved by a network of frontostriatal regions, including the ventral striatum, ventral caudate nucleus, and medial prefrontal cortex\(^5-9\), responds during the anticipation/prediction of action-related outcomes (e.g., cue-outcome contingencies). The habit system, subserved by corticostriatal regions, including the putamen and premotor cortex\(^9-12\), regulates automatic responses triggered by environmental cues or emotional states (e.g., stimulus–response associations). When actions become stimulus-bound, they continue in an outcome-insensitive manner\(^13, 14\). Chronic exposure to stimulant drugs have been shown to disrupt the balance between the goal-directed\(^9, 15-18\) and habit-based\(^3, 4, 9, 19, 20\) systems in stimulant drug addiction.

While stimulant drug addiction is associated with blunted brain responses to non-drug reward cues, there is evidence for heightened neural responses during exposure to
drug cues (21, 22). This underscores the role of incentive context, whereby drug-related rewards may compensate for deficits in dopaminergic responsivity (23, 24). The monetary incentive delay task (MIDT) is a well-validated paradigm that assesses neural responses underlying the anticipation and receipt of predicted rewarding outcomes (8, 25) relevant for goal-directed behaviour. The distinct phases of the MIDT provide the very framework to examine how the manipulation of incentive context (drug and non-drug) can reveal disparate neural changes during reward anticipation and receipt in stimulant use disorder (SUD) patients. Support for this dissociation may point to a bias in neural responses that favours drug-related goals (26-28) due to a predominance of drug cue-related mesolimbic dopaminergic reactivity (21, 22, 29, 30) across brain networks.

The brain has characteristics of large-scale complex networks (31), in which functional connectivity between multiple distributed regions can vary during psychological processes relevant to addiction, such as reward. Examining the dynamic properties of brain networks can reveal more widespread disturbances that go undetected when using conventional analytical methods. Latent disturbances in brain network connectivity have been reported in addiction populations (32-36), thus underscoring the validity of this approach to detecting more prevalent disruptions in neural processing in addiction disorders. The aim of this study, therefore, was to 1) compare the efficiency of brain networks underpinning the anticipation and receipt of drug and non-drug rewards in SUD patients and healthy control participants, and 2) examine the influence of stimulant drug exposure on functional network architecture in SUD patients. Considering the importance of context in the anticipation of reward, relevant for goal-directed behaviour, we hypothesized that differences in incentive context (drug and non-drug) induces disparate changes in connectivity in SUD patients and
control participants. We predicted that SUD patients would show reduced functional connectivity during the anticipation of monetary reward, but normal or increased connectivity during the anticipation of drug-related reward. Given that the receipt of reward is also critical for goal-directed behaviour, we further predicted divergent processing of reward outcomes during drug and non-drug-related contexts.

Material and Methods

Participants

Forty-eight control participants (mean age 32.5±1.3 SEM; 63% male) and 41 patients with stimulant drug dependence (subsequently referred to as stimulant use disorder (SUD), mean age 34.7±1.2 SEM; 90% male) completed the study. Screening procedures are documented elsewhere(37-39), but will also be summarised here briefly. All participants underwent a clinical interview to ascertain the clinical diagnosis of stimulant drug dependence using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders(40). Data were also collected on participants' personal and family history of substance use, physical health (including signs of acute intoxication and withdrawal), and mental health history. Exclusionary criteria included a lifetime history of a psychotic, neurological, or neurodevelopment disorders, and traumatic head injury for any participant. Control participants were excluded for a history of drug and alcohol addiction (except nicotine) and a positive drug urine sample prior to scanning. SUD patients were active compulsive stimulant drug users, as recorded using the obsessive-compulsive drug use scale (mean±SEM=23.6±1.5), and as confirmed by stimulant-positive urines. SUD patients met DSM-IV criteria dependence for amphetamines (7%), cocaine (32%) or crack-cocaine (61);
22% of which reported intravenous use. SUD patients also showed co-dependency to cannabis (10%), opiates (54%) and alcohol (29%). Controls were healthy with low levels of drug and alcohol use, as reflected by low scores on the alcohol use disorder identification test (mean±SEM=3.23±0.33) and drug use questionnaire (mean±SEM=0.0±0.0). The study was approved by the NHS Cambridgeshire Research Ethics Committee (08/H0308/310 PI: KDE), and written informed consent was obtained from all participants prior to study enrolment. The study was conducted in accordance with the Declaration of Helsinki.

**Money and Drug Incentivization Task (MDIT)**

The MDIT(37, 38) consisted of one monetary and one drug incentive run, each of which were counterbalanced across participants with respect to their order. While the stimuli displayed differed between the monetary and drug incentive contexts, the task structure remained the same. This involved cue-anticipation, visual target response, and response outcome feedback phases. There was a total of 66 trials in each incentive run. Dependent measures were accuracy (percentage) and mean reaction time (milliseconds) to the visual target on each trial type. All participants initially completed 66 practice trials with both incentive types prior to scanning to familiarize them with the task.

**Functional MRI (fMRI) Data Acquisition**

Images were collected on a Siemens TIM Trio 3-Tesla scanner (Erlangen, Germany) at the Wolfson Brain Imaging Centre, Cambridge (UK). A more detailed description of the acquisition parameters can be found in the supplementary methods section.
fMRI Data Analyses

Data pre-processing and statistical analysis were conducted using FEAT (fMRI Expert Analysis Tool) from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl). Pre-statistical processing was as follows: motion correction utilizing FMRIB's Linear Image Registration Tool (MCFLIRT); non-brain matter removal using Brain Extraction Tool (BET); spatial smoothing with a 5-mm full-width half maximum Gaussian kernel; mean-based intensity normalization; nonlinear high-pass temporal filtering (Gaussian-weighted least squares straight line fit, with sigma=25.0 sec). The six rigid body movement parameters were also included as regressors in the model. First level whole-brain mixed-effects analyses were performed by modelling the MDIT anticipation periods (money, neutral-money, drug, neutral-drug) as explanatory variables within the context of the general linear model on a voxel-by-voxel basis (variable boxcar functions for the cue+variable anticipation period regressors were convolved with the haemodynamic response function). The drug and money outcome feedback periods (collapsed across successful and unsuccessful trials) were also modelled (stick functions for trial period regressors were convolved with the haemodynamic response function). During these first level analyses, the money anticipation>neutral money anticipation; money outcome>neutral money outcome; drug anticipation>neutral drug anticipation, and drug outcome>neutral drug outcome contrasts were formulated. Cluster (Gaussianised T) statistical images were determined using a variety of cluster forming thresholds ($Z>2.3$ and $3.1$) and $p<0.05$ (FWE) corrected for multiple comparisons during within groups (one-sample-tests) and between groups (unpaired t-tests) analyses. All analyses were conducted while controlling for gender.
FEAT was also used to generate a time series for each phase of the MDIT for each participant, which also involved formulating the same condition contrasts. This yielded unique voxel-wise contrast of parameter estimate (COPE) images that reflected the magnitude of the hemodynamic response evoked by each of these conditions. This yielded a time series that contained 44 unique COPE images for each drug/money anticipation and drug/money outcome contrast.

**Time Series Extraction and Correlation Matrices**

Using the brainnetome atlas (210 cortical and 36 subcortical nodes) as our connectome of interest\(^{(41)}\), we extracted the mean COPE value time series from each of the 246 anatomical regions of interest (ROI) for the money cue-anticipation, money outcome, drug cue-anticipation, and drug outcome contrasts for each participant. Pearson correlation coefficient analyses were then conducted on these ROI time series outputs to construct whole brain ROI-to-ROI pairwise matrices in MATLAB.

**Functional Connectivity**

Group comparisons in ROI-to-ROI connectivity across matrices were first assessed using the Network Based Statistics (NBS) Toolbox\(^{(42)}\) in MATLAB. Comparisons between the CON and SUD groups were conducted using unpaired t-test analyses to identify graph sub-components of regions across the connectome of interest that showed differences in connectivity between the two groups for each contrast of interest. Graph sub-components
were identified among the connections using a t-statistic threshold $t > 3.1$. From here, a family-wise error (FWE) corrected $p$-value ($p < 0.05$) was calculated for the size of each resulting component using permutation testing (5000 permutations). All analyses were conducted while controlling for gender.

Network visualisation

Brain connectivity maps and circular connectograms were generated using the NeuroMArVL software (www.immersive.erc.monash.edu.au/neuromarvl).

Graph Theory Measures

The network property of characteristic path length was estimated from each participant’s correlation matrix using the GraphVar (www.rfmri.org/GraphVar) toolbox for functional brain connectivity(43) in MATLAB. Characteristic path length is the minimum number of edges that must be traversed to go from one node (brain region) to another in a network. For a pair of nodes that are nearest neighbours, the path length is 1. Path length describes how well integrated the network is with respect to information exchange.

Other Statistics

Group demographics were compared using simple unpaired t-test analyses or Fisher’s exact tests. ANCOVA analyses were conducted on MDIT performance and graph theory metrics, controlling for gender. Pearson correlation analyses were conducted to test for associations between years of stimulant use and neurobehavioural measures where the
CON and SUD groups significantly differed. All these analyses were conducted using the R statistical software package (www.R-project.org). A more detailed description of these, and all other (behavioural, fMRI, connectivity) analysis methods can be found in the supplementary methods section.

Results

Demographics

Table 1 shows demographic and questionnaire data for both groups. The groups were balanced for age, income, verbal intelligence, and their sensitivity to financial value, as assessed by a visual analogue scale (never–always) on which participants had to rate how likely they were to pick up money from the ground. The groups did significantly differ on other measures, such as mood, smoking status, and gender distribution. Given the imbalance in gender distribution, and evidence for gender differences in reward system functioning (44), particularly in addiction (45, 46), all neurobehavioral analyses reported below controlled for gender.

MDIT

For the monetary incentive run, there was a significant effect of condition for accuracy ($F_{173, 1} = 10.13; p < 0.01; \text{Money} > \text{Neutral}, \text{Figure 1A}$) and reaction time ($F_{173, 1} = 5.22; p < 0.05; \text{Money} < \text{Neutral}; \text{Figure 1B}$). For the drug incentive run, there was also a significant effect of condition for accuracy ($F_{173, 1} = 5.1; p < 0.05; \text{Drug} > \text{Neutral}; \text{Figure 1C}$), but
no effect of condition for reaction time (Figure 1D). No main effects of group were identified in these analyses, suggesting that both groups were equally engaged to perform the task.

**fMRI**

Whole brain analyses showed that the control and SUD patient groups activated a frontostriatal network of regions during money anticipation (Figures S1A and B). During drug anticipation, there was a disparate pattern of activation change, whereby SUD patients clearly engaged frontostriatal regions, particularly the ventral striatum and orbitofrontal cortex that was not seen in the control group (Figures S2A and B). Between groups unpaired t-tests did not reveal any significant differences between the controls and SUD patients for money and drug anticipation, however (See Supplementary section for a full description of all fMRI results).

**Functional Connectivity**

During the money anticipation phase, a sub-network comprising 110 connections and involving 82 regions \( p=0.002 \) emerged where the SUD patients had significantly less connectivity compared to the control group (Figure 2). Most of these connections (53%) were inter-hemispheric, with 28% confined to the right hemisphere and 19% to the left hemisphere. The frontal module had the highest number of regions (30%) in this network, with the temporal module having the highest number of connections (30%), most of which were with regions in the frontal module (21%). There was no evidence for group differences in connectivity during the drug anticipation phase.
SUD patients also showed significantly less connectivity during monetary outcome processing (Figure 3) in a sub-network consisting of 85 connections and involving 54 regions ($p=0.02$). Most of these connections (50%) were inter-hemispheric, with 18% confined to the right, and 32% confined to the left hemispheres. The frontal module had the highest number of regions (39%), and the highest number of connections (50%), most of which were with regions in the subcortical module (36%).

SUD patients also had significantly less connectivity during drug outcome processing (Figure 4) across a sub-network comprising 104 connections and involving 59 regions ($p=0.02$). Most of these connections (47%) were inter-hemispheric, with 22% restricted to the right, and 31% to confined to the left. The frontal module had the highest number of regions (41%), followed by the subcortical module (29%). Most connections across this network were also between regions in the frontal and subcortical modules (73%).

**Graph Theory Measures**

Significant group differences for path length across these networks are also reported (Supplementary Figs 6 A, B and C).

**Correlations**

There were significant correlations between the duration of stimulant use in SUD patients and path length for the money anticipation network ($r_{39}=0.4, p<0.05$, Figure 5A); money outcome network ($r_{39}=0.42, p<0.01$, Figure 5B), and drug outcome network ($r_{39}=0.4, p<0.05$, Figure 5C).
Discussion

This study investigated brain network connectivity during the anticipation and processing of reward outcomes in SUD patients and healthy controls. We investigated the role of incentive context on network connectivity using two different types of rewards: drug-related and monetary reward. As hypothesised, we found that SUD patients showed significantly reduced functional connectivity during the anticipation of monetary reward, but not during the anticipation of drug reward, in accordance with the notion of drug-related cues having obtained incentive salience that overrides the value of non-drug rewards (26-28).

Decreased functional connectivity during monetary, but not drug-related, reward anticipation in SUD

SUD patients showed significantly less connectivity compared with controls across a network largely involving frontal, temporal, limbic and subcortical regions. This difference in network connectivity emerged in the absence of any group differences on MDIT performance and reported reward value sensitivity. Given that reward anticipation is relevant for goal-directed behaviour, our findings are consistent with prior work
showing abnormal goal-directed functional networks in abstinent addicted patients (32). Importantly, this network where SUD patients showed less connectivity featured regions such as the ventral and dorsal caudate, portions of the anterior cingulate gyrus (e.g. bilateral caudodorsal region) and medial prefrontal cortices; all of which are known to be involved in motivational processes that support goal-directed behaviour (8, 47-51). While addiction is generally associated with blunted brain responses (15-17, 52) and connectivity deficits (32, 53) during reward processing, there is evidence for heightened neural responses (21, 22, 29, 30, 54, 55) and increased connectivity (55-59) during exposure to drug cues. Reduced network connectivity during monetary reward anticipation in SUD patients emerged in the absence of any group network connectivity differences during drug reward anticipation, suggesting an uncoupling of network connectivity that is specifically related to a non-drug context. This suggests connectivity impairments during the anticipation of non-drug rewards, but not for drug rewards, which may explain a bias previously seen in other addiction samples (26-28). The implication here is that the system can work normally, but only for drug-related incentives, and hence lead to a narrowing of goals.

**Decreased functional connectivity during reward outcomes in SUD, irrespective of context**

The current task involved the trial-by-trial monitoring of outcomes regarding success or failure to procure drug and non-drug rewards. SUD patients demonstrated significantly less connectivity in response to both monetary and drug reward outcomes compared with controls. This group difference involved networks, encompassing regions of frontal and
subcortical modules. There was a notable and dominant flow of connectivity across these two networks that involved the prefrontal cortex (dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate gyrus), basal ganglia (ventral caudate, globus pallidus), and the thalamus; regions that have been reported to respond during the processing of rewarding and punishing feedback in healthy control populations (25, 50, 60-62) and which are reported as hypofunctional in addiction populations (52, 63, 64). One notable inclusion in these networks was the thalamus, which is known to play a critical role in the transmission and processing of corticocortical information through the relaying and integration of signals between cortical and subcortical structures (65, 66). There are also prominent connections between the thalamus and regions involved in goal-directed behaviour and action evaluation, such as the medial and orbitofrontal cortices (67), and the thalamus is considered an important interface between the ventral striatopallidum and the dorsal striatum (68). The disruptions in connectivity observed here may suggest a breakdown in thalamocortical circuitry (69, 70), supporting the contention that there exists a general deficit in connectivity involving a thalamocortical network for processing reward outcomes in stimulant drug addiction. This observation is interesting because the insensitivity to outcome may facilitate the development of habits.

**Duration of stimulant drug use associated with disruptions to global network integration**

The graph theory measure of path length was extracted from the regions of the monetary reward anticipation and monetary and drug reward outcome networks. This was done to elucidate its possible contribution to the group differences in functional network connectivity that emerged. SUD patients had significantly longer path lengths compared with
controls across these networks. Shorter path lengths are an indicator of integration, demonstrating how easily information can be transferred across regions of a network (71), with significantly longer path lengths also reported in other addiction populations (32, 72, 73). The initial findings of from the NBS analyses, therefore, may represent a deficient mobilization of long-range information exchange between brain regions of these networks that is critical for maintaining global connectedness during reward processing. Interestingly, path length across these networks correlated with the duration of stimulant use in SUD patients. This may point to increasing levels of stimulant drug exposure as a potential factor in these functional network differences.

Possible implications of network abnormalities in SUD

Reductions in money anticipation-related connectivity reported in our SUD patients may be due to lapses in attention and/or working memory. We observed that the right inferior temporal gyrus (ITG) had a disproportionately high number of connections across the money anticipation network. These connections were predominantly with regions in frontal, limbic and subcortical modules. The ITG plays a critical role in mediating visual working memory (74, 75), with the encoding of multiple cue-outcome contingencies likely requiring stimulus information to be held online during the monetary incentive run of our task. Reductions in connectivity involving the ITG may suggest a disruption to working memory in SUD patients that obstructs the correct encoding and subsequent transfer of information to frontal, limbic and subcortical regions.
The non-specific uncoupling of connectivity observed during both drug and money reward outcomes may point to neural impairments related to reinforcement learning (i.e., aberrant outcome prediction errors signalling). While our task did not involve any requirement for contingency response learning (i.e., the contingencies were instructed beforehand), it has been found that learning signals are still generated when associations are well known(76), with several studies having examined the neural correlates of trial-by-trial prediction errors using monetary incentive delay tasks(77-79). There have also been reports of deficits in the neural correlates of prediction error signalling in addiction populations(80-82). Dysconnectivity in the current sample during reward outcome processing involved regions such as the dorsolateral prefrontal cortex, medial and lateral orbitofrontal cortices, dorsal anterior cingulate gyrus, and ventral caudate, all of which are involved in the encoding of prediction errors(83-87). This non-specific context dysconnectivity during reward outcome, therefore, could be the result of suboptimal updating of valence outcomes.

Alternatively, dysconnectivity during outcome phases could also represent differences in adaptive processing on the MDIT. We observed that the average BOLD activation patterns during money and drug reward outcomes elicited a clear divergence in the direction of brain responses, with SUD patients activating and the controls predominantly deactivating across multiple regions. Widespread deactivation across brain regions in the control group may be due to lower but more widespread neuronal activity during the outcome phase. This may reflect adaptive processes during task engagement(88), which translates into greater connectivity across brain networks. Disturbances in reallocating neural resources to efficiently encoding cue-reward associations in SUD patients, however, may maintain a “surprise” signal during reward outcomes, and this hypothetically suppresses deactivation patterns across more
widespread regions of the brain (89). This could translate into less connectivity across networks and lead to attentional problems for predictive cues (i.e., reward outcomes are encoded as being more surprising). This is consistent with an impaired goal-directed system which does not guide behaviour based on outcomes.

Reduced connectivity during monetary reward anticipation, relevant for motivated behaviour, concomitant with dysconnectivity during reward outcome processing, may facilitate the formation of habitual control in SUD patients. This is because habits do not require motivation and are insensitive to outcomes (13, 14, 90). Reductions in network connectivity in SUD patients may also have arisen due to anatomical changes across these networks. Given the link between functional and anatomical connectivity (91-93), and reported research findings of structural brain deficits in stimulant addiction (94-96), it is conceivable that the observed differences may involve abnormalities at specific regions across these networks.

**Strengths and weaknesses**

This study has several strengths. We used the task structure of a well-validated reward paradigm to assess not only anticipation of monetary incentives, but also drug-related incentives in SUD patients and healthy controls. Both groups had relatively large sample sizes for neuroimaging studies, were well-matched on task performance, and on their sensitivity of task monetary reward values. We have also employed a novel analytical approach to assess latent widespread disruptions across underlying brain networks that departs from merely attempting to investigate disturbances in activation. The presence of connectivity differences across distributed networks, concomitant with differences on the
topological network measure of path length, is also a noteworthy strength of the study. To our knowledge, this is the first study in SUD patients to compare the attribution of “motivational salience” across drug and non-drug incentive contexts to reveal a dissociation in the neural substrates of reward anticipation across brain networks, and non-specific connectivity impairments in outcome processing. We were unable to separately investigate differences in network connectivity with respect to reward receipt and reward omissions across the two incentive conditions in our analyses, due to the variable (performance-dependent) number of events for the outcome periods. Therefore, network group differences for the reward outcome conditions cannot be exclusively attributed to responses related to reward or punishment. While the group differences on anxiety and mood likely reflect the clinical endophenotype of SUD patients (97), we cannot unequivocally dismiss their potential influence on group differences in brain connectivity. We also acknowledge that a multiple comparisons correction was not applied to some of the between groups analyses.

**Conclusion**

This study has undertaken an empirical assessment of differences in salience attribution by comparing SUD patients with control participants during drug and non-drug reward anticipation and outcome processing. The results suggest impairments in brain systems implicated in monetary reward anticipation relevant for goal-directed behaviour. The anticipation of drug-reward (not real drugs), however, seems to normalise impairments this system. This is consistent with the clinical phenotype of SUD that is associated with reduced motivation for goal-directed outcome, unless it is related to drugs. This may lead to a narrowing towards drug-related goals. Our results further reveal a significant dysfunction
across networks implicated in reward outcome processing, irrespective of context. This finding is consistent with the notion of a generalised predominance of habitual control in SUD, which acts independently from outcome, providing further support for a habit bias in SUD patients. This habit bias may also explain why many patients continue using drugs, even in the absence of pleasure and in presence of adverse consequences.

Declaration of Conflicting Interests
The authors report no biomedical financial interests or potential conflicts of interest.

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References


Figure legends.

Figure 1. Task performance for the control (CON) and stimulant use disorder (SUD) groups showing A) mean accuracy (**p<0.01 Money>Neutral), and B) mean reaction time (*p<0.05 Money<Neutral) on the monetary incentive run; and C) mean accuracy (*p<0.05 Drug>Neutral), and d) mean reaction time on the drug incentive run.

Figure 2. Connectivity differences emerging from a non-parametric network-based statistics (NBS) analysis showing where SUD patients demonstrated significantly less connectivity compared to the control participants during monetary reward anticipation. Reductions in connectivity in SUD patients are represented by A) brain connectivity maps and B) a circular connectogram. T=top view; B=bottom view.

Figure 3. Connectivity differences emerging from a non-parametric network-based statistics (NBS) analysis showing where SUD patients demonstrated significantly less connectivity compared to the control participants during monetary reward outcomes. Reductions in connectivity in SUD patients are represented by A) brain connectivity maps and B) a circular connectogram. T=top view; B=bottom view.

Figure 4. Connectivity differences emerging from a non-parametric network-based statistics (NBS) analysis showing where SUD patients demonstrated significantly less connectivity compared to the control participants during drug reward outcomes. Reductions in connectivity
in SUD patients are represented by A) brain connectivity maps and B) a circular connectogram. 
T=top view; B=bottom view.

Figure 5. Correlations between reported stimulant use in the SUD group and characteristic 
path length in A) the money anticipation network (r39)= -4, p=0.01); B) money outcome 
network (r39)=.42, p<0.01), and C) drug outcome network (r39)= .4, p=0.01).
Table 1. Showing the demographic, questionnaire, and substance use results for the control (CON) and substance use disorder (SUD) groups. Group comparisons were conducted using either independent samples t-tests or Fisher’s exact tests. Data are expressed as mean ± standard error mean.

<table>
<thead>
<tr>
<th></th>
<th>CON</th>
<th>SUD</th>
<th>Statistics</th>
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<tbody>
<tr>
<td>Gender (male/female) a</td>
<td>30/18</td>
<td>37/4</td>
<td>p&lt;0.01</td>
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<td>Age (years)</td>
<td>32.5 ± 1.3</td>
<td>34.7 ± 1.2</td>
<td>t=1.25, df=87, p=0.22</td>
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<td>Income (£/month)</td>
<td>659.6 ± 135.7</td>
<td>399.2 ± 104.9</td>
<td>t=1.58, df=87, p=0.14</td>
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<td>Verbal Intelligence (NART)</td>
<td>112.1 ± 1.2</td>
<td>110.6 ± 1.1</td>
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<td>Depression (BDI-II total score)</td>
<td>2.2 ± 0.4</td>
<td>17.7 ± 1.9</td>
<td>t=8.89, df=87, p&lt;0.001</td>
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<td>Trait anxiety (STAI-T score)</td>
<td>29.7 ± 0.8</td>
<td>46.1 ± 1.9</td>
<td>t=8.43, df=87, p&lt;0.001</td>
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<td>OCDUS score</td>
<td>0.0 ± 0.0</td>
<td>23.6 ± 1.5</td>
<td>t=17.54, df=87, p&lt;0.001</td>
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<td>Impulsivity (BIS-11 score)</td>
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<td>77.3 ± 1.4</td>
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<td>Smokers (never/current/former) a</td>
<td>21/6/21</td>
<td>1/38/2</td>
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<td>Duration of stimulant drug use (years)</td>
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<td>16.1 ± 1.0</td>
<td>t=17.227, df=87, p&lt;0.001</td>
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<td>Sensitivity to Financial Value b</td>
<td>71.4 ± 3.7</td>
<td>76.1 ± 4.2</td>
<td>F=0.729; df=86, 1; p=0.4</td>
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</tbody>
</table>

a Fisher’s exact test used.
b Values of 10p and 50p measured using visual analogue scales before being averaged.

Beck Depression Inventory (BDI-II) Questionnaire.
State Trait Anxiety Inventory (STAI-T) Questionnaire.
Obsessive Compulsive Drug Use Scale (OCDUS).
Barratt Impulsiveness Scale (BIS-11).
Network Modules

- Frontal
- Temporal
- Parietal
- Insula
- Limbic
- Occipital
- Subcortical
Network Modules
- Frontal
- Temporal
- Parietal
- Insula
- Limbic
- Occipital
- Subcortical
Network Modules

- Frontal
- Temporal
- Parietal
- Insula
- Limbic
- Occipital
- Subcortical

A) Frontal
B) Temporal
C) Parietal
D) Insula
E) Occipital
F) Limbic
G) Subcortical

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