ARCHIVAL REPORT

Abnormal Brain Networks Related to Drug and Nondrug Reward Anticipation and Outcome Processing in Stimulant Use Disorder: A Functional Connectomics Approach

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ABSTRACT

BACKGROUND: Drug addiction is associated with blunted neural responses to nondrug 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, which may reflect a narrowing toward 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 participants (n = 48) on network connectivity related to anticipation and outcome processing using a modified monetary incentive delay task. We hypothesized increased task-related activation and connectivity to drug rewards in patients with SUD, and reduced task-related activation and connectivity to monetary rewards during incentive processing across brain networks.

RESULTS: In the presence of behavioral and regional brain activation similarities, we found that patients with SUD showed 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 patients with SUD had longer path lengths across these networks, all of which positively correlated with the duration of stimulant drug use.

CONCLUSIONS: Specific disruptions in connectivity in networks related to the anticipation of nondrug reward together with more general dysconnectivity in the processing of rewarding outcomes suggest an insensitivity to consequences. These observations support the notion of a predominance of habitual control in patients with SUD.

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Stimulant drug addiction is a growing public health problem that leads to major economic and health burdens, which are difficult to treat (1). Identifying and understanding disturbances 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 behaviors typically seen in stimulant-addicted individuals because they affect the interplay between two regulatory brain systems that are critical for control over behavior: the incentive-driven, goal-directed system and the stimulus-bound habit system.

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 has 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 (9).

While stimulant drug addiction is associated with blunted brain responses to nondrug 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 rewards.
predicted rewarding outcomes (8,25) relevant for goal-directed behavior. The distinct phases of the MIDT provide the very framework to examine how the manipulation of incentive context (drug and nondrug) can reveal disparate neural changes during reward anticipation and receipt in stimulant use disorder (SUD). Support for this dissociation may point to a bias in neural responses that favors 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 addicted populations (32–36), thus underscoring the validity of this approach to detecting more prevalent disruptions in neural processing in addictive disorders. The aims of this study, therefore, were to (1) compare the efficiency of brain networks underpinning the anticipation and receipt of drug and nondrug rewards in patients with SUD and healthy control participants and (2) examine the influence of stimulant drug exposure on functional network architecture in patients with SUD. Considering the importance of context in the anticipation of reward, relevant for goal-directed behavior, we hypothesized that differences in incentive context (drug and nondrug) would induce disparate changes in connectivity in patients with SUD and control participants. We predicted that patients with SUD 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 behavior, we further predicted divergent processing of reward outcomes during drug- and nondrug-related contexts.

METHODS AND MATERIALS

Participants
Forty-eight control participants (mean age ± SEM, 32.5 ± 1.3 years; 63% male) and 41 patients with stimulant drug dependence (subsequently referred to as SUD; age 34.7 ± 1.2 years; 90% male) completed the study. Screening procedures are documented elsewhere (37–39) but are briefly summarized here. 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 neurodevelopmental disorders, and traumatic head injury for any participant. Control participants were excluded for a personal and family history of drug and alcohol addiction (except nicotine) and a positive drug urine sample prior to scanning. Patients with SUD were active stimulant drug users with moderate to severe levels of compulsive using patterns, as reflected by the Obsessive Compulsive Drug Use Scale (mean ± SEM: 23.6 ± 1.5) and confirmed by stimulant-positive urine samples. All patients with SUD met DSM-IV criteria dependence for amphetamines (7%), cocaine (32%), or crack cocaine (61%), 22% of whom reported intravenous use. Some patients with SUD also had a co-dependency to cannabis (10%), opiates (54%), and alcohol (29%). Control participants were healthy with low levels of drug and alcohol use, as reflected by low scores on the Alcohol Use Disorders Identification Test (mean ± SEM: 0.0 ± 0.0). The study was approved by the National Health Service Cambridgeshire Research Ethics Committee (08/H0308/310 PI:KDE), and written informed consent was obtained from all participants prior to study enrollment. The study was conducted in accordance with the Declaration of Helsinki.

Monetary Incentive Delay Task
The MIDT (37,38) consisted of one monetary and one drug incentive run, which were counterbalanced across participants with respect to 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 (in 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 themselves with the task.

Functional Magnetic Resonance Imaging Data Acquisition
Neuroimaging data were collected on a Siemens TIM Trio 3T scanner at the Wolfson Brain Imaging Centre (Cambridge, United Kingdom). A more detailed description of the acquisition parameters can be found in the Supplemental Methods.

Functional Magnetic Resonance Imaging Data Analyses
Data preprocessing and statistical analysis were conducted using FEAT from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsf). Prestatistical processing was as follows: motion correction utilizing FMRIB’s Linear Image Registration Tool (MCFLIRT), non-brain matter removal using BET (Brain Extration Tool), spatial smoothing with a 5-mm full width at half maximum Gaussian kernel, mean-based intensity normalization, and nonlinear high-pass temporal filtering (Gaussian-weighted least-squares straight line fit, with sigma = 25.0 seconds). The six rigid body movement parameters were also included as regressors in the model. First-level whole-brain mixed-effects analyses were performed by modeling the MIDT 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 hemodynamic response function).
Abnormal Brain Networks in Stimulant Use Disorder

The drug and money outcome feedback periods (collapsed across successful and unsuccessful trials) were also modeled (stick functions for trial period regressors were convolved with the hemodynamic 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 (Gaussianized $T$) statistical images were determined using a variety of cluster-forming thresholds ($Z > 2.3$ and $3.1$) and $p < .05$ (familywise error) corrected for multiple comparisons during within-groups (1-sample tests) and between-groups (unpaired $t$ tests) analyses. All analyses were conducted while controlling for biological sex.

FEAT was also used to generate a time series for each phase of the MIDT for each participant, which also involved formulating the same condition contrasts. This yielded unique voxelwise contrast of parameter estimate images that reflected the magnitude of the hemodynamic response evoked by each of these conditions. In turn, this yielded a time series that contained 44 unique contrast of parameter estimate 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 contrast of parameter estimate value time series from each of the 246 anatomical regions of interest (ROIs) 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 version 2021b (The MathWorks, Inc.).

Functional Connectivity
Group comparisons in ROI-to-ROI connectivity across matrices were first assessed using the Network-Based Statistics Toolbox (42) in MATLAB. Comparisons between the control and SUD groups were conducted using unpaired $t$-test analyses to identify graph subcomponents of regions across the connectome of interest that showed differences in connectivity between the two groups for each contrast of interest. Graph subcomponents were identified among the connections using a $t$ statistic threshold of $t > 3.1$. From here, a familywise error-corrected $p$ value ($p < .05$) was calculated for the size of each resulting component using permutation testing (5000 permutations). All analyses were conducted while controlling for sex.

Network Visualization
Brain connectivity maps and circular connectograms were generated using the NeuroMArVL software (https://immersive.erc.monash.edu/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 neighbors, 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. Analyses of covariance were conducted on MIDT performance and graph theory metrics, controlling for sex. Pearson correlation analyses were conducted to test for associations between years of stimulant use and neurobehavioral measures in which the control and SUD groups significantly differed. All these analyses were conducted using the R statistical software package version 4.1.2 (R Foundation for Statistical Computing). A more detailed description of these and all other (behavioral, functional magnetic resonance imaging, connectivity) analysis methods can be found in the Supplemental Methods.

RESULTS
Demographics
Table 1 shows demographic and questionnaire data for both groups. The groups were balanced for age, disposable income, education, drug use, and other characteristics.

| Table 1. Demographic, Questionnaire, and Substance Use Results for the CON and SUD Groups |
|---------------------------------|---------|---------|---|
| CON | SUD | Statistic |
|---|---|---|
| Sex, Female/Male$^a$ | 18/30 | 4/37 | $p < .01$ |
| Age, Years | $32.5 \pm 1.3$ | $34.7 \pm 1.2$ | $t_{87} = 1.25$, $p = .22$ |
| Disposable Income, $\$/Month | $659.6 \pm 135.7$ | $399.2 \pm 104.9$ | $t_{87} = 1.58$, $p = .14$ |
| Verbal Intelligence, NART | $112.1 \pm 1.2$ | $110.6 \pm 1.1$ | $t_{87} = 0.91$, $p = .36$ |
| Depression, BD-II Total Score | $2.2 \pm 0.4$ | $17.7 \pm 1.9$ | $t_{87} = 8.89$, $p < .001$ |
| Trait Anxiety, STAI-T Score | $29.7 \pm 0.8$ | $48.1 \pm 1.9$ | $t_{87} = 8.43$, $p < .001$ |
| OCDUS Score | $0.0 \pm 0.0$ | $23.6 \pm 1.5$ | $t_{87} = 17.54$, $p < .001$ |
| Impulsivity, BIS-11 Score | $59.3 \pm 1.1$ | $77.3 \pm 1.4$ | $t_{87} = 10.02$, $p < .001$ |
| Smoker, Never/Current/ Former | 21/6/21 | 1/38/2 | $p < .001$ |
| Duration of Stimulant Drug Use, Years | $0.0 \pm 0.0$ | $16.1 \pm 1.0$ | $t_{87} = 17.227$, $p < .001$ |
| Sensitivity to Financial Value$^b$ | $71.4 \pm 3.7$ | $76.1 \pm 4.2$ | $F_{1,86} = 0.7291$, $p = .4$ |

Values are presented as $n$ or mean $\pm$ SEM. Group comparisons were conducted using either independent samples $t$ tests or Fisher’s exact tests.

BDI-II, Beck Depression Inventory, Second Edition; BIS-11, Barratt Impulsiveness Scale Version 11; CON, control group; NART, National Adult Reading Test; OCDUS, Obsessive Compulsive Drug Use Scale; STAI-T, State-Trait Anxiety Inventory, Trait Version; SUD, stimulant use disorder group.

$^a$Fisher’s exact test used.

$^b$Values of 10 pence and 50 pence measured using visual analog scales before being averaged.
income, verbal intelligence, and their sensitivity to financial value. The latter was assessed using a visual analog scale (ranging from "never" to "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 sex distribution. Given the imbalance in sex distribution, and evidence for sex differences in reward system functioning (44), particularly in addiction (45,46), all neurobehavioral analyses reported below controlled for sex.

Monetary Incentive Delay Task
For the monetary incentive run, there was a significant effect of condition for accuracy ($F_{1,173} = 10.13, p < .001$; money > neutral) (Figure 1A) and reaction time ($F_{1,173} = 5.22, p < .05$; money < neutral) (Figure 1B). For the drug incentive run, there was also a significant effect of condition for accuracy ($F_{1,173} = 5.1, p < .05$; drug > neutral) (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.

Functional Magnetic Resonance Imaging
Whole-brain analyses showed that the control and SUD groups activated a frontostriatal network of regions during money anticipation (Figure S1A, B). During drug anticipation, there was a disparate pattern of activation change such that patients with SUD relied on frontostriatal regions, particularly the ventral striatum and orbitofrontal cortex—a pattern that was not seen in control participants (Figure S2A, B). However, between-group unpaired t tests did not reveal any significant differences between the control participants and patients with SUD for money and drug anticipation (see the Supplement for a full description of all functional magnetic resonance imaging results).

Functional Connectivity
During the money anticipation phase, a subnetwork comprising 110 connections and involving 82 regions ($p = .002$) emerged in which the patients with SUD had significantly less connectivity compared with the control participants (Figure 2). Most of these connections (53%) were interhemispheric, 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.

Patients with SUD also showed significantly less connectivity during monetary outcome processing (Figure 3) in a subnetwork consisting of 85 connections and involving 54 regions ($p = .02$). Most of these connections (50%) were interhemispheric, with 18% confined to the right hemisphere and 32% confined to the left hemisphere. The frontal module had the highest number of regions (39%) and the highest

Figure 1. Task performance for the control (CON) and stimulant use disorder (SUD) groups showing (A) mean accuracy ($***p < .001$; money > neutral) and (B) mean reaction time ($p < .05$; money < neutral) on the monetary incentive run and (C) mean accuracy ($p < .05$; drug > neutral) and (D) mean reaction time on the drug incentive run.
number of connections (50%), most of which were with regions in the subcortical module (36%).

Patients with SUD also had significantly less connectivity during drug outcome processing (Figure 4) across a subnetwork comprising 104 connections and involving 59 regions ($p = .02$). Most of these connections (47%) were interhemispheric, with 22% restricted to the right hemisphere and 31% confined to the left hemisphere. 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 (Figure S6A–C).

**Correlations**

There were significant correlations between the duration of stimulant use in patients with SUD and path length for the money anticipation network ($r_{39} = 0.4, p < .05$) (Figure 5A), money outcome network ($r_{39} = 0.42, p < .01$) (Figure 5B), and drug outcome network ($r_{39} = 0.4, p < .05$) (Figure 5C).

**DISCUSSION**

This study investigated brain network connectivity during the anticipation and processing of rewarding outcomes in patients with SUD and healthy control participants. We investigated the role of incentive context on network connectivity using two different types of rewards: drug-related and monetary. As hypothesized, we found that patients with SUD 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 nondrug rewards (26–28).

**Decreased Functional Connectivity During Monetary, but Not Drug-Related, Reward Anticipation in SUD**

Patients with SUD showed significantly less connectivity compared with control participants 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 MIDT performance and reported reward value sensitivity. Given that reward...
anticipation is relevant for goal-directed behavior, our findings are consistent with prior work showing abnormal goal-directed functional networks in abstinent addicted patients (32). Importantly, this network in which patients with SUD 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 behavior (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 patients with SUD 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 nondrug context. This suggests connectivity impairments during the anticipation of nondrug 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 brain 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 nondrug rewards. Patients with SUD demonstrated significantly less connectivity in response to both monetary and drug reward outcomes compared with control participants. 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 participants (25,50,60–62) and that are reported as hypofunctional in addicted patients (52,63,64).

One notable inclusion in these networks was the thalamus, which is known to play a critical role in the transmission and

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**Figure 3.** Connectivity differences emerging from a nonparametric network-based statistics analysis showing where patients with stimulant use disorder (SUD) demonstrated significantly less connectivity compared with the control participants during monetary reward outcomes. Reductions in connectivity in patients with SUD are represented by (A) brain connectivity maps and (B) a circular connectogram. B, bottom view; CG, cingulate gyrus; FuG, fusiform gyrus; hiP3, posterior intraparietal area; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; MFG, medial frontal gyrus; MTG, medial temporal gyrus; OFC, orbital frontal cortex; PCG, posterior cingulate gyrus; PCL, paracentral lobule; PEm, medial precuneus; PFop, rostroventral inferior parietal lobule area 40; PPh, inferior parietal lobule rostromedial area 40; Pga, rostroventral inferior parietal lobule area 39; SFG, superior frontal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; T, top view; V5/MT+, visual motion area.
There are also prominent connections between the thalamus and regions involved in goal-directed behavior 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. Patients with SUD had significantly longer path lengths compared with control participants 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 addictions (32,72,73). The initial findings of from the Network-Based Statistics 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 patients with SUD. 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 patients with SUD may be due to lapses in attention and/or working memory. We observed that the right inferior temporal gyrus 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 inferior temporal gyrus 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 inferior temporal gyrus may suggest a disruption to working memory in patients with SUD that obstructs the correct encoding and subsequent transfer of information to frontal, limbic, and subcortical regions.

The nonspecific 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 signaling). 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 MIDTs (77–79). There have also been reports of deficits in the neural correlates of prediction error signaling 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 nonspecific 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 MIDT. We observed that the average blood oxygen level–dependent activation patterns during money and drug reward outcomes elicited a clear divergence in the direction of brain responses, with patients with SUD activating and the control participants 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 translate into greater connectivity across brain networks. Disturbances in reallocating neural resources to efficiently encode cue–reward associations in patients with SUD, 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 that does not guide behavior based on outcomes.

Reduced connectivity during monetary reward anticipation, relevant for motivated behavior and concomitant with dysconnectivity during reward outcome processing, may facilitate the formation of habitual control in patients with SUD. This is because habits do not require motivation and are insensitive to outcomes (13,14,90). Reductions in network connectivity in patients with SUD 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.

Figure 5. Correlations between reported stimulant use in the stimulant use disorder group and characteristic path length in (A) the money anticipation network ($r_{39} = -0.4, p = .01$), (B) the money outcome network ($r_{39} = 0.42, p < .01$), and (C) the drug outcome network ($r_{39} = 0.4, p = .01$).
Abnormal Brain Networks in Stimulant Use Disorder

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 patients with SUD and healthy control participants. Both groups had relatively large sample sizes for neuroimaging studies and 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 patients with SUD to compare the attribution of motivational salience across drug and nondrug incentive contexts to reveal a dissociation in the neural substrates of reward anticipation across brain networks and nonspecific 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 patients with SUD (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.

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

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Abnormal Brain Networks in Stimulant Use Disorder

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