Reduced Behavioral and Neural Activation in Stimulant Users to Different Error Rates during Decision Making

Martin P. Paulus, Kathryn L. Lovero, Marc Wittmann, and David S. Leland

Background: Behavioral processes and neural systems dysfunctions that put individuals at risk for drug use in general, and stimulant use in particular, are poorly understood. Here, the hypothesis is examined that stimulant-using subjects adjust their decision making less as a function of errors as evidenced by attenuated behavioral and neural substrate activation patterns.

Methods: Twelve young adults who had used stimulants were compared with 12 education-matched, stimulant-naïve comparison subjects. Subjects completed the two-choice prediction task with three fixed error-rate conditions (20%, 50%, or 80% errors) during functional magnetic resonance imaging.

Results: Stimulant users relative to comparison subjects showed less strategy adjustment to different error rates, for example, they were less likely to stay with winning responses (win-stay) and to shift away from losing responses (lose-shift). These subjects also showed different activation patterns as a function of error rate in left insular and bilateral dorsolateral prefrontal cortex but not anterior cingulate. The degree to which individuals adjusted switching rate, or win-stay/lose-shift consistent responses, as a function of errors was correlated with the difference in insular cortex activation differences between high and low error rates.

Conclusions: The behavior of stimulant users is less adaptive to the frequency of errors made and fewer brain processing resources are deployed during decision making to anticipate erroneous performance. These findings could be markers for the predisposition of drug taking; however, their relevance for development of drug dependence requires further study.

Key Words: Decision making, error processing, fMRI, insula, stimulants

Stimulant (i.e., amphetamine and cocaine) dependence is an important public health problem with an estimated lifetime prevalence of 1%–3% (1–3). The rate of any illicit drug use increases during adolescence and peaks between 18 to 25 years of age, when approximately 20% of college students report some level of illicit drug use (other than marijuana) and approximately 10% report having used stimulants over the past year (4). Results from twin studies are consistent with the notion that genetic factors, which may be disorder-specific (5), predispose to drug use and account for up to 60% of drug-using behavior (6).

Studying individuals who have used stimulants but do not have extended experience with them or suffer from significant adverse consequences associated with substance use may provide an opportunity to examine what cognitive and affective characteristics may predispose individuals to transition from recreational use of the drug to abuse or dependence. Previously (7), stimulant-using individuals showed increased activation in the caudate, an area involved in processing salient events (8), in response to uncertainty. Personality measures revealed that users were more impulsive than comparison subjects and that neural response to uncertainty in a number of areas including the thalamus/caudate was positively correlated with impulsivity. These results suggested that these individuals may be subject to more “action pressure,” that is, have an increased urge to act, when making decisions under uncertainty.

Decision making consists of a complex set of processes that are presumed to be orchestrated within various brain systems to find an optimal outcome. When people are asked to respond on decision-making tasks in the laboratory, subjects typically choose the response that is associated with the highest anticipated reinforcement, that is, they select an action that is most likely to result in a “correct” outcome or yield the highest reward (9–11). This behavior is consistent with the notion that anticipated “success” or “failure” critically influences decision-making (12). In simple choice decision-making tasks, reinforcement frequency and payoffs primarily determine response selection (13) in such a way that subjects adjust their response strategy consistent with an error-correction set of rules (14). In short, people compute the expected utility, that is, weighted average between expected success and failure, and choose the alternative that has the most favorable success over failure weight.

This study was aimed to examine whether stimulant-using individuals show an altered response to different error rates. We hypothesized that behaviorally these individuals would show an attenuated adjustment to different error rates. We expected that this attenuated adjustment would be correlated with altered activation in the anterior insula, anterior cingulate, and/or dorsolateral prefrontal cortex, areas which have been implicated in the anticipatory processing and executive planning of actions following errors (15,16). Support for these hypotheses would provide further evidence that individuals who have used stimulants show altered decision-making behavior and neural systems activation patterns.

Methods and Materials

Participants

This study was approved by the University of California San Diego (UCSD) Institutional Review Board. All subjects were interviewed face-to-face using a structured diagnostic interview (SCID) (17), modified to enable us to document the use of illicit

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substances. Twelve young adults (aged 20.0 years, SD 2.6) who had used stimulants at least twice in the last 6 months were compared with 12 education-matched stimulant-naive comparison subjects (aged 18.3 years, SD 0.9). Stimulant users were recruited from flyers and Internet advertisements. They reported having used cocaine, amphetamines, or other stimulant drugs when not prescribed but were not other treatment-seeking nor stimulant-dependent. Subjects were instructed to abstain from illicit substance use for 48 hours before the experimental session. All subjects were trained to perform the two-choice prediction task before testing during functional magnetic resonance imaging (fMRI) scanning and received $50 for participation. No restrictions were placed on the consumption of caffeine-containing beverages; none of the subjects were smokers.

Measures
Subjects completed the Zuckerman Sensation Seeking Scale (SSS Form V) (18) and the Barratt Impulsivity Scale (BIS-11) (19). The SSS is a questionnaire to assess engagement in high-risk activities (20). The items are grouped to form the subscales of thrill and adventure seeking, experience seeking, disinhibition, and boredom susceptibility. The BIS measures various components of impulsivity, notably the three subscales of nonplanning impulsivity, motor impulsivity, and attention/cognition impulsivity (21).

Task
The two-choice prediction task (22–24) has been used previously to examine the effect of past history of outcomes and choice behavior on selecting the current choice (Supplement 1). In this version of the task, the number of “correct” or “incorrect” trials in a block of trials (i.e., the block’s error rate was determined a priori). Three error rate block types were presented in the same order for each subject: high (80% of responses were “incorrect”), chance-level (50% of responses were “incorrect”), and low (20% of responses were “incorrect”). Blocks were separated by a resting condition (presentation of the background stimulus, no response required), which lasted between 6 and 12 sec.

Behavioral Measures
For each trial, the participant’s selection (right or left) and response latency, as well as the outcome (right or left), were obtained. Decision-making strategies were assessed using two sets of measures, one for general response biases and one for the influence of prior task events on current responses. General response bias was assessed both by the number of left versus right responses and by the number of stay responses (i.e., same response as previous trial—left following left or right following right) versus switch responses (i.e., response opposite that of previous trial—left following right or right following left). The degree to which a current selection was determined by the previous selection, the previous outcome, or a combination of both was assessed using mutual information functions (25) (Supplement 1).

fMRI Protocol and Image Analysis Pathway
Magnetic resonance images were obtained using a 1.5-Tesla whole-body system (Siemens, Erlangen). Anatomic T1-weighted images of the whole brain (MPRAGE, repetition time [TR] = 11.4 msec, echo time [TE] = 4.4 ms, flip angle 10°, field of view [FOV] 256 × 256, 1 mm³ voxels) were obtained sagittally. Thirty-two slices of T2*-weighted images were obtained in the axial plane using gradient-recalled echo-planar imaging (TE = 40 msec, flip angle 90°, 64 × 64-pixel FOV = 256 × 256 mm, 4-mm contiguous slice thickness) every 3000 msec for 128 repetitions, yielding a voxel size of 4 mm³.

All structural and functional image processing was done with the Analysis of Functional Neuroimages software package (AFNI) package (26). A multivariate regression approach was used to relate changes in echoplanar image intensity (EPI) to differences in task characteristics. Stimulant subjects did not differ from comparison subjects on motion during scanning: t_{droll}(22) = −.737, p = .469; t_{dyaw}(22) = 1.488, p = .151; t_{dpitch}(22) = −.822, p = .420; t_{dtheta}(22) = −.881, p = .388; t_{dxaw}(22) = −.316, p = .759; and t_{dxaw}(22) = −.940, p = .358. The time series of motion parameters were used to obtain an average for these six motion parameters for each subject. For the analysis, only three motion parameters (droll, dpitch, dyaw) were used as regressors to adjust EPI intensity changes due to motion artifacts because for small changes, the change in the roll, pitch, and yaw are linearly related to x, z, and y changes, respectively. Three regressors of interest (20%, 50%, and 80% error rate blocks) were convolved with a gamma variate function that models a prototypical hemodynamic response and normalized. Percent signal change was calculated from the multiple regressor analysis and used as the main dependent measure. Planned contrasts were for the activation difference between 20% and 80% error rate were used to determine success versus failure, that is, the change of brain activation as a function of error-rate change. A Gaussian filter with full width at half maximum (FWHM) of 6 mm was applied to voxelwise percentage signal change data or to the linear contrasts to account for individual variations of the anatomical landmarks. A threshold adjustment method based on Monte-Carlo simulations was used to guard against identifying false-positive areas of activation (27).

A simulation was conducted with a voxelwise p < .01, a spatial correlation equal to the FWHM, and a connectivity radius of 4 mm showed that a voxelwise a priori probability of .01 would result in an a posteriori voxelwise probability of 4.219 × 10⁻⁷ and a corrected clusterwise probability of false-positive detection of .01 if a minimum volume of 768 μL (or 12 connected voxels) was considered. The Talairach Demon software (28) was used to determine brain labels for activation clusters.

Statistical Analysis
All behavioral analyses were carried out with SPSS 12.0 (29). A 2 × 3 mixed-model multivariate analysis of variance (ANOVA), with error rate (20%, 50%, or 80%) as the within-subjects factor and group (stimulant user versus control) as the between-subjects factor, was used to analyze the behavioral measures. Averages of neural activation patterns extracted from the functional regions of interest identified by the planned contrasts were subjected to a secondary ANOVA with error rate as a fixed factor and subjects as a random factor. Because there was a slight difference in age across groups, all ANOVA analyses were covaried for age. Parametric correlational analyses were conducted to determine whether differences in brain activation were related to behavioral differences during the task or to personality characteristics of the participants. Significant correlations between brain activation and behavior or personality characteristics were followed up with regression analysis to determine the degree to which lifetime stimulant or tetrahydrocannabinol (THC) use affected this relationship. Only those correlations that remained significant after controlling for these factors are reported.
Results

Drug Usage and Behavioral Assessments

Based on the Structured Clinical Interview for DSM and questionnaire lifetime assessments, stimulant users had used amphetamine-like stimulants an average of 36 times (range: 0–240) and/or cocaine an average of 14 times (range: 0–40); they had used any type of stimulants for an average of 51 times (range: 2–240). Although individuals were recruited on the basis of their stimulant use, all of these individuals had used other illicit drugs (Table 1). In particular, stimulant users had used THC an average of 316 times (range: 12–900). None of the comparison subjects reported having used THC or other illicit drugs. Stimulant users scored higher than comparison subjects on Thrill and Adventure Seeking, as well as Experience Seeking, two facets of the Zuckerman Sensation Seeking Scale (Table 2). These individuals also exhibited higher levels of Attentional and Motor impulsiveness, which are subscales of the BIS.

Two-Choice Prediction Task—Behavioral Results

Stimulant users and comparison subjects made an average of 21.3 ± 1.5 and 21.7 ± 1.5 responses per error rate block and took an average of 834 ± 89.5 and 869 ± 89.5 msec to make a selection. Neither the number of responses nor the response latency was significantly affected by error rate. Moreover, there was no significant group difference or group by error rate interaction (Supplement 1). There was a slight but significant bias for all participants to select right more frequently than left. Although there was no overall effect of error rate on switching rates, there was a significant group by error rate interaction. As shown in Figure 1B, whereas comparison subjects showed the expected increase of switching rate as a function of error rate, stimulant users consistently showed a higher switch rate and differed significantly from comparison subjects for the 20% error rate condition. Moreover, increased switching at 20% error rate was significantly correlated with both thrill and adventure seek-

<table>
<thead>
<tr>
<th>Type</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine-Like Stimulants (amphetamines, methamphetamine, prescription stimulants, etc.)</td>
<td>38.6</td>
<td>66.4</td>
<td>0–240</td>
</tr>
<tr>
<td>Cocaine</td>
<td>14.1</td>
<td>12.7</td>
<td>0–40</td>
</tr>
<tr>
<td>Marijuana</td>
<td>316.5</td>
<td>300.9</td>
<td>12–900</td>
</tr>
<tr>
<td>Hallucinogens (LSD, mescaline, peyote, MDA, DMT, STP, psilocybin, etc.)</td>
<td>3.6</td>
<td>1.7</td>
<td>0–6</td>
</tr>
<tr>
<td>PCP</td>
<td>3.0</td>
<td>2.8</td>
<td>0–5</td>
</tr>
<tr>
<td>Barbiturates, Librium (or valium)-Type Drugs or Downers (not prescribed)</td>
<td>2.7</td>
<td>2.1</td>
<td>0–5</td>
</tr>
<tr>
<td>Opiates (heroin, prescription pain medication etc.)</td>
<td>4.0</td>
<td>4.1</td>
<td>0–10</td>
</tr>
<tr>
<td>Inhalants (glue, aerosols, toluene, gasoline, paint, etc.)</td>
<td>3.7</td>
<td>3.8</td>
<td>0–8</td>
</tr>
</tbody>
</table>

Table 2. Personality Characteristics

<table>
<thead>
<tr>
<th>Measures</th>
<th>Comparison Subjects (n = 12)</th>
<th>Stimulant Users (n = 12)</th>
<th>t test</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSS Thrill and Adventure Seeking</td>
<td>6.17 ± 2.48</td>
<td>7.91 ± 1.14</td>
<td>−2.131</td>
<td>.045a</td>
</tr>
<tr>
<td>Experience Seeking</td>
<td>4.58 ± 2.35</td>
<td>7.36 ± 1.57</td>
<td>−3.302</td>
<td>.003a</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>5.08 ± 2.97</td>
<td>6.84 ± 2.59</td>
<td>−1.506</td>
<td>.147</td>
</tr>
<tr>
<td>Boredom Susceptibility</td>
<td>1.67 ± 1.30</td>
<td>1.83 ± 1.40</td>
<td>−0.287</td>
<td>.777</td>
</tr>
</tbody>
</table>

BIS, Barratt Impulsivity Scale; SSS, Sensation Seeking Scale.

aSignificant p values.
ing ($r = .519, p = .009$) and attentional impulsivity ($r = .559, p = .006$).

A significant group effect for cross-mutual information (i.e., the mutual information between participant selections and prior outcomes) was because choices by stimulant users were significantly less influenced by the previous trial outcome than those of comparison subjects. In comparison, there was no group difference in the degree to which the previous response influenced the selection on the current trial. Stimulant users made significantly fewer selections according to a win-stay/lose-shift strategy than comparison subjects, that is, they selected fewer win-stay and lose-shift consistent responses (Supplement 1). Stimulant users did not modulate the degree to which they selected a win-stay/lose-shift consistent response as a function of error rate (Figure 1C). In contrast, comparison subjects selected a win-stay/lose-shift consistent response significantly less often during high (80%) error rate blocks compared with the 20% and 50% blocks, reflected by a significant group by error interaction (Supplement 1). Thus, stimulant users changed response options less as a function of varying error rates and were less influenced by a win-stay/lose-shift strategy.

**Functional Neuroimaging Results**

Both groups showed activation differences as a function of error rate in bilateral caudate and bilateral temporal gyrus (Table 3). Similar to previous studies (30,31), activation in these structures was significantly less for the 80% relative to 20% error rate. There was a group effect in error-rate related activation in left insula and bilateral middle frontal gyrus. Whereas comparison subjects showed an increase of left insula activation as a function of error rate (greater activation at high error rates), stimulant users showed the reverse pattern, a greater activation at the low compared with the high error rates (Figure 2). Moreover, comparison subjects, but not stimulant users, showed an error-rate-dependent increase in bilateral middle frontal gyrus. There was no significant activation difference in the anterior cingulate cortex.

**Brain-Behavior Relationships**

Correlational analyses (followed by regression analyses to covary for the amount of stimulants and THC used) were performed between areas of significant brain activation difference across groups and between personality measures and behavioral response patterns in the two-choice prediction task. The degree to which individuals reduced win-stay/lose-shift consistent responses as a function of error rate was inversely correlated with adjustments in left insular cortex activation according to error rate ($r = -.53, p = .007$, Figure 3A). Specifically, the more individuals abandoned a win-stay/lose-shift consistent response at higher error rates the greater insular cortex activation attenuated as a function of error rate. This relationship remained significant when controlling for lifetime use of marijuana (beta = -.142, $p = .45$) or lifetime use of stimulants (beta = -.365, $p = .05$), which had a marginally significant effect. Lower Experience Seeking was associated with more modulation of bilateral prefrontal cortex activation (right:

<table>
<thead>
<tr>
<th>Volume</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>L/R</th>
<th>Description</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2048</td>
<td>-32</td>
<td>-8</td>
<td>-1</td>
<td>L</td>
<td>Caudate/putamen</td>
<td>39</td>
</tr>
<tr>
<td>1856</td>
<td>38</td>
<td>-51</td>
<td>5</td>
<td>R</td>
<td>Middle temporal gyrus</td>
<td>39</td>
</tr>
<tr>
<td>1280</td>
<td>38</td>
<td>-33</td>
<td>37</td>
<td>R</td>
<td>Inferior parietal lobule</td>
<td>40</td>
</tr>
<tr>
<td>1024</td>
<td>40</td>
<td>-68</td>
<td>17</td>
<td>R</td>
<td>Middle temporal gyrus</td>
<td>39</td>
</tr>
<tr>
<td>896</td>
<td>44</td>
<td>-48</td>
<td>18</td>
<td>R</td>
<td>Superior temporal gyrus</td>
<td>13</td>
</tr>
<tr>
<td>896</td>
<td>3</td>
<td>34</td>
<td>48</td>
<td>R</td>
<td>Superior frontal gyrus</td>
<td>8</td>
</tr>
<tr>
<td>832</td>
<td>18</td>
<td>8</td>
<td>13</td>
<td>R</td>
<td>Caudate</td>
<td></td>
</tr>
<tr>
<td>768</td>
<td>-51</td>
<td>-18</td>
<td>9</td>
<td>L</td>
<td>Transverse temporal gyrus</td>
<td>41</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group × Error Rate</th>
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<tbody>
<tr>
<td>6016</td>
</tr>
<tr>
<td>896</td>
</tr>
<tr>
<td>896</td>
</tr>
<tr>
<td>768</td>
</tr>
</tbody>
</table>

Labels and Brodmann area (BA) designations are based on Talairach Demon software (28).

![Figure 2](image_url). Different activation to error rate. Stimulant-using individuals show an inverse relationship between error rate and brain activation in left insula (upper right) and bilateral middle frontal gyrus (lower left and right).
Discussion

This investigation yielded four main results. First, stimulant users relative to comparison subjects adjusted their choices less as a function of different error rates. Second, these subjects also showed an altered activation pattern in the left insular and bilateral dorsolateral prefrontal cortex, but not the anterior cingulate, as a function of error rate. Third, brain pattern differences were associated with an attenuated change in win-stay/lose-shift consistent responses. Fourth, relatively more experience seeking, as part of increased tendency to engage in sensation seeking, was associated with less prefrontal cortical activation adjustment as a function of error rates. Therefore, when stimulant users relative to comparison subjects chose responses that led to an erroneous prediction they showed less behavioral adjustment and fewer changes in brain processing resources. Together with increased activation to uncertainty (7), this attenuated error processing may constitute a second altered cognitive process during decision making.

The behavioral results of an attenuated switching response as a function of error rate and fewer win-stay/lose-shift consistent responses in stimulant-using individuals relative to comparison subjects are in contrast with behaviors previously observed in methamphetamine-dependent individuals (25). There are several possible explanations. First, the group of stimulant-using individuals was not dependent and had relatively few exposures to stimulant. Therefore, the findings with methamphetamine-dependent individuals could point toward a long-term use effect. Second, only approximately one of seven individuals who use stimulants goes on to develop stimulant dependence (32). Thus, our group of users may comprise individuals who have different behavioral characteristics than individuals who have experienced many years of use and dependence. Users in this study exhibited an increased switching rate regardless of previous outcomes and error rates, which could be related to impulsivity and sensation seeking. Moreover, because only a subset of individuals develops dependence, one may speculate that the opposite behavioral pattern found here may actually point toward resiliency factors. Specifically, the behavioral characteristics of our group may represent mostly individuals who are not going to develop dependence and may therefore not show the same behavioral patterns as those observed in dependent users.

To summarize, attenuated error processing and decreased use of win-stay/lose-shift consistent responses may reflect characteristic of drug initiation behaviors but not maintenance or misuse behaviors. However, these hypotheses can only be tested longitudinally by comparing those individuals who develop dependence with those who do not.

The degree to which failure or success influence behavioral change, particularly response selection during decision making, may be an important process that requires further investigation in stimulant-using subjects. The inverse relationship between the degree of behavioral change and insular functioning, even after controlling for the amount of stimulant and THC use, may point toward an attenuated or altered signal in this structure. There is accumulating evidence that the insular cortex is important for processing both aversive (33) and reward-related stimuli (34). The insular cortex is important for subjective feeling states and interoceptive awareness (35,36). Within the insular cortex, a multidimensional representation and integration of the current and possibly the predicted (37) body state provides the individual with a temporal representation of a “global moment in time” (A.D. Craig, personal communication, July 21, 2006). Importantly, this interoceptive network processes information in a homeostatic manner, that is, the valence of the information fundamentally depends on the nature of the individual’s current state. Thus, altered insular cortex activity as a function of error rate may point toward altered interoceptive processing in response to errors. A recent study of individuals with brain lesions showed that those who had insular damage were more likely to experience a disruption of cigarette addiction, including abstinence of the urge to smoke (38). The insular cortex is also part of inhibitory processing together with the middle and inferior frontal gyri, frontal limbic areas, and the inferior parietal lobe (39). In the context of an inhibitory task, individuals with high error rates showed increased insula response (40). Error-related processing during a go–nogo task was associated with activation in the insula among other neural structures such as the anterior cingulate cortex, presupplementary motor area, thalamus, and right inferior parietal lobule (41). Others have suggested that left and right anterior insular cortex are active only during error processing but not during response competition, inhibition, selection, or execution (42). Taken together, these imaging studies support the notion that the insular cortex may have a monitoring function for correct performance and appropriate response strategies to adjust to the subject’s homeostatic state.

Stimulant use in our group was found to occur in the context of other drug use, which is consistent with other studies in both drug users (43,44) and drug-dependent individuals (45). Therefore, one has to be cautious in directly relating the findings of this
study to the use of amphetamine-like stimulants or cocaine. Moreover, other studies have shown that stimulant users who also used other illicit drugs had increased odds of progressing into dependence (45). Although the stimulant user sample for this study was selected on the basis of a history of any lifetime use, the use data indicate that, on average, individuals had used stimulants (combined amphetamine-like stimulants or cocaine) only 50 times in their lives. Thus, it is unlikely that the personality and symptom differences between the groups are a consequence of drug use.

This investigation has several limitations. First, the group sizes were relatively small, which may affect our ability to detect smaller effects and to delineate relationships between behavior brain activation patterns and stimulant use. Second, the two-choice prediction task has been criticized for not providing explicit rewards (e.g., money or primary reinforcers for correct versus incorrect choices) and the fact that individual’s response patterns do not affect the degree to which subjects can make successful predictions. Nevertheless, we have repeatedly shown that despite the lack of an optimal response strategy, individuals do not engage in random choices but tend to follow simple but predictable response patterns (24,46,47). Third, this investigation implemented a block-design version of this task, which does not enable us to delineate different processes involved in decision making. We have argued previously (48) that fast or slow event-related designs will be necessary to better determine whether stimulant users show altered assessment, selection, or outcome processing abnormalities. Fourth, although individuals were instructed not to use any substances within 48 hours of scanning and reported that they had not, we cannot rule out the possibility that acute substance use contributed to the findings because we did not obtain a urine toxicology screen at time of testing.

In conclusion, this study shows that stimulant-using individuals who are not dependent adjust behavior and neural substrates less than comparison subjects in response to errors on a simple decision-making task. The attenuated representation of an adverse outcome has two consequences. First, it fails to reduce the likelihood to select the same choice in the future, that is, alter switching behavior as a function of error rates. Second, it facilitates the selection of responses with potential adverse outcomes, that is, deviation from a win-stay/lose-shift consistent response strategy toward risk-taking behavior. Future investigations using larger groups will need to determine the degree to which these findings are specific for individuals using stimulants or whether these behavioral and neural substrate patterns are a factor contributing to drug use in general.

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