Craving versus Control: Negative Urgency and Neural Correlates of Alcohol Cue Reactivity

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Highlights

1. Negative urgency is associated with alcohol abuse yet the mechanisms remain unknown.
2. Negative urgency correlated with greater caudate nucleus activity to alcohol cues.
3. Negative urgency's relation to alcohol abuse may be due to greater alcohol craving.

Contributors

DSC, CND, RM, and DRL developed the study concept and methodology. DSC collected and analyzed data. DSC, CDN, RM, and DRL drafted and approved the manuscript.

Conflict of Interest

No conflict declared

Abstract

Background. Alcohol abuse is a common and costly practice. Individuals high in negative urgency, the tendency to act rashly when experiencing negative emotions, are at particular risk for abusing alcohol. Alcohol abuse among individuals high in negative urgency may be due to (a) increased activity in the brain's striatum, (b) decreased activity in brain regions associated with self-control, or (c) a combination of the two.

Methods. Thirty eight non-alcohol-dependent participants completed a measure of negative urgency and then underwent functional magnetic resonance imaging (fMRI) while passively viewing pleasant and alcohol images.

Results. Alcohol images (as compared to pleasant images) were associated with activation in the caudate nucleus, a brain region associated with linking reward to external stimuli. Negative urgency (above and beyond other facets of impulsivity) correlated positively with this caudate activation in response to alcohol images. Alcohol images and negative urgency were unassociated with activity in the lateral prefrontal cortex, a self-regulatory brain region.

Conclusions. These findings provide initial support that the alcohol abuse observed among individuals high in negative urgency may be due, in part, to heightened reactivity in the striatum to alcohol. Investigating such neural contributors to self-regulation failure is crucial to reducing substance abuse.

Keywords: negative urgency, alcohol, caudate nucleus, self-regulation, fMRI

Introduction

One facet of impulsivity, negative urgency, is characterized by rash behavior during negative affect, is robustly associated with alcohol abuse (Magid and Colder, 2007; Settles, Cyders, and Smith, 2010; Whiteside and Lynam, 2001). The literature is largely silent as to the mechanisms through which negative urgency promotes alcohol abuse. Using functional neuroimaging, we sought to fill this gap.

1.1 The UPPS model of Impulsivity

Whiteside and Lynam (2001) identified four distinct factors of impulsivity that include negative urgency (U), lack of premeditation (P), lack of perseverance (P), and sensation-seeking (S). Several studies have confirmed a five-factor structure of the UPPS-P, including *positive* urgency, which is impulsive reactivity to *positive* affect (-P; Lynam and Miller, 2004; Smith, Fischer, Cyders, Annus, and Spillane, 2007).

1.2 Negative Urgency and Alcohol Abuse

Negative urgency correlates with increased alcohol abuse above and beyond other facets of impulsivity (Magid and Colder, 2007; Settles et al., 2010; Whiteside and Lynam, 2001). But why do individuals high in negative urgency succumb to alcohol abuse? Self-regulation failures in the context of negative urgency are often explained as due to insufficient inhibition (e.g., Wilbertz et al., 2014). This reflects a more general trend to focus on inhibitory failure (e.g., Muraven and Baumeister, 2000). This emphasis on 'top-down' restraint ignores a significant 'bottom-up' process: craving (Hoffmann and Van Dillen, 2012). Malfunctions of self-regulation, such as alcohol abuse, could be due to a lack of self-regulatory restraint, heightened craving, or the simultaneous presence

of the two (Hofmann and Van Dillen, 2012; Inzlicht and Schmeichel, 2012). These two

processes arise in different regions of the brain.

1.3 Neural Correlates of Alcohol Cue Reactivity

      1.3.1 Caudate Nucleus. The caudate nucleus is a subcortical structure in the

dorsal striatum. This neural region links anticipated reward with behavior intended to

achieve that reward (Knutson and Cooper, 2005). Activation of the caudate nucleus is

associated with experimental inductions of alcohol craving, (Modell and Mountz, 1995),

and is also positively correlated with self-reported alcohol cravings (Hommer, 1999).

Alcohol-dependent individuals demonstrate increased activation of the left caudate

nucleus in response to alcohol images, as compared to healthy controls (Heinz et al.,

2004). Although these findings were observed among alcohol dependent individuals,

the caudate is a crucial neural substrate of the formation of associations between novel

stimuli (e.g., alcohol) and the experience of reward (Yin and Knowlton, 2006). Taken

together, these findings suggest that the caudate plays a unique and reliable role in the

desire to consume alcohol. Negative urgency has been previously linked to greater

alcohol reactivity in other brain regions that are part of the same dopaminergic reward

circuitry that includes the caudate (i.e., the ventromedial prefrontal cortex; Cyders et al.,

2014; for a review of neural systems involved in negative urgency see Smith & Cyders,

under review).

      1.3.2 DLPFC. The dorsolateral prefrontal cortex (DLPFC) is a brain area

regarded as the biological substrate of psychological processes necessary for

successful self-regulatory restraint (see Banfield, Wyland, Macrae, Munte, and

Heatherton, 2004). DLPFC stimulation reduced self-reported alcohol craving (Boggio et al., 2008). Thus, the DLPFC appears to regulate alcohol cravings.

1.4 Overview

We predicted that negative urgency, independent of other facets of impulsivity, would be *positively* associated with alcohol-specific activation of the caudate nucleus. Conversely, we predicted that negative urgency, independent of other facets of impulsivity, would be *negatively* associated with alcohol-specific activation of the DLPFC. To test these hypotheses, participants completed a measure of impulsivity that included its five facets of negative urgency, lack of premeditation, lack of perseverance, sensation-seeking, and positive urgency. Then, participants viewed alcohol and pleasant images while undergoing fMRI.

2. Material and Methods

2.1 Participants

Participants were 40 healthy, right-handed undergraduates who received course credit and $65 (see Supplemental Materials for exclusion criteria). One participant was excluded from analyses because of distorted functional magnetic resonance imaging (fMRI) data. Another participant was deemed an outlier (see Results). Analyses were therefore performed on the 38 remaining participants (19 females; Age: $M = 18.95$, $SD = 1.33$).

2.2 Procedure

2.2.1 Pre-scan. Participants completed a demographics questionnaire, a screening form to ensure safety and comfort in the MRI environment, the Alcohol Use Disorders Identification Test (AUDIT; Barbor, La Fuente, Saunders, and Grant, 1992), a

one-year Timeline Follow-Back Calendar of alcohol use (Sobell and Sobell, 1992), and the UPPS-P Impulsivity Scale (Lynam, Smith, Whiteside, and Cyders, 2006). The AUDIT and calendar measures of alcohol abuse were used to establish participants' histories of drinking behavior. Participants then practiced the cue reactivity task and were placed in the scanner.

2.2.2 Cue reactivity task. While undergoing fMRI, participants completed a simple cue reactivity paradigm in which they passively viewed images depicting either alcohol, marijuana, polydrugs (e.g., cocaine), or control images that were neutral or pleasant. Alcohol, marijuana, and polydrug stimuli were acquired from published research on the appetitive nature of drugs and alcohol (Mun, von Eye, Bates, and Vaschillo, 2008; Buckman, White, and Bates, 2010; Ray, Hanson, Hanson, and Bates, 2010). Neutral and pleasant images were taken from the International Affective Picture Set (IAPS; Lang, Bradley, and Cuthbert, 2008). All images were pre-rated in the IAPS technical report along a 1 - 9 Likert scale on the dimensions of pleasantness (Lang et al., 2008).

Pleasant images included a diverse array of stimuli (e.g., appetizing food) and were rated as highly pleasant ($M = 7.53$, $SD = 0.26$). Each block of the task sequentially presented five images of a single condition (4 seconds per image, 20 seconds total). This was then followed by 10 seconds of a fixation crosshair. The task contained 21 blocks, which were divided into 3 alcohol, 3 marijuana, and 3 polydrug blocks that were matched with 9 pleasant blocks. Three neutral blocks were also included. The order of block-conditions was randomized but held constant across participants. Full details

regarding MRI data acquisition, preprocessing, analysis, and region-of-interest construction are available in the Supplemental Materials.

3. Results

3.1 Descriptives

No participants exhibited alcohol dependence, as evidenced by AUDIT scores below the cutoff of 20 (range: 0 – 12, M = 3.50, SD = 3.33). For the year previous to the study, participants showed wide variability in the number of drinks they indicated on the alcohol calendar (range: 0 – 732 drinks; M = 92.94, SD = 156.87). All five subscales of the UPPS inventory were sufficiently reliable (αs = .74 - .84) and showed substantial variability (see Supplemental Table 1). Males reported greater negative urgency than females, t(36) = 2.16, p = .037.

3.2 Neuroimaging

Alcohol images, compared with pleasant images, related to increased activity in the left head of the caudate nucleus [Figure 1; 60 contiguous voxels, maximum Z = 3.33, MNI peak coordinates (x, y, z) = -16, 22, 6]. This same contrast failed to elicit any voxels of significant activation in either hemisphere of the DLPFC and thus we were unable to assess urgency's relation with activity in this region.

Figure 1. Left caudate nucleus activation associated with alcohol > pleasant images. Coordinates are MNI.
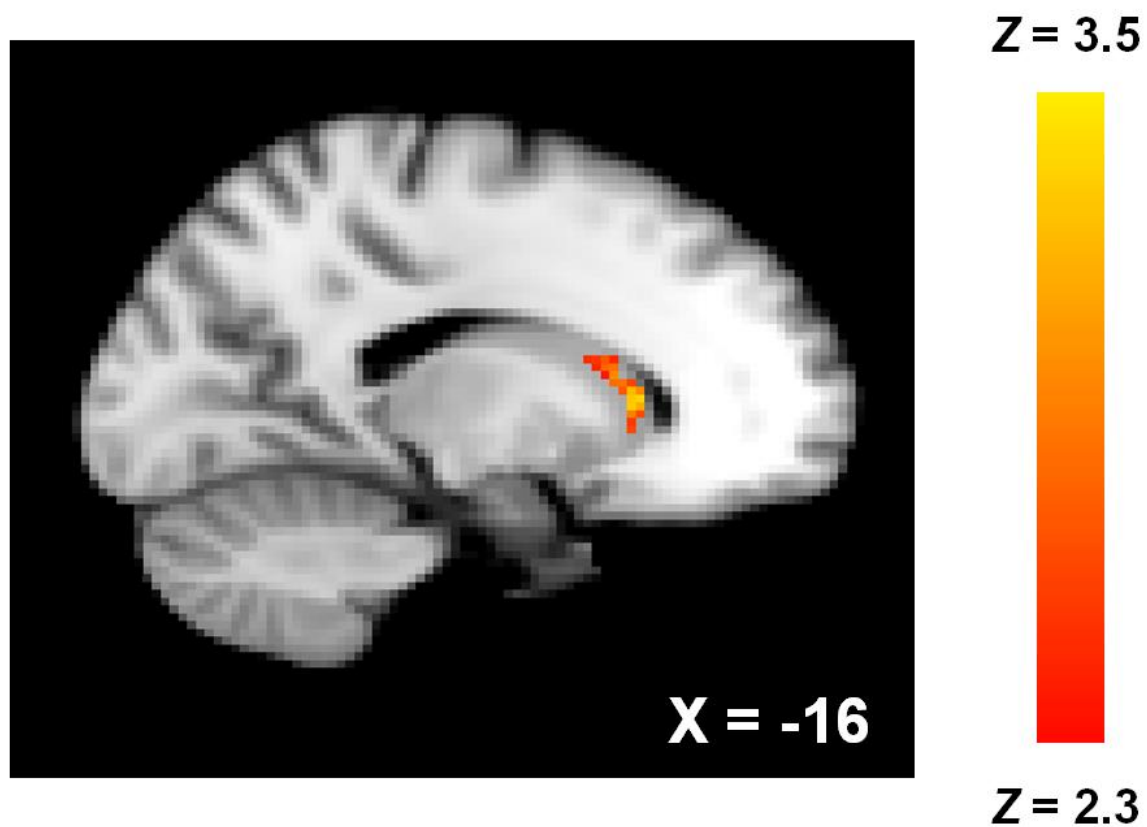
Functional data from the activated main effect cluster in the caudate nucleus (alcohol > pleasant contrast) were converted to units of percent signal change and extracted (as outlined by Mumford, J. http://*mumford.fmripower.org/perchange_guide.pdf*). Males exhibited marginally greater caudate reactivity to alcohol images, $t(36) = 1.85$, $p = .073$. Whole brain analyses (alcohol > pleasant) revealed a large cluster of activity in the occipital cortex, potentially suggesting greater visual attention to alcohol stimuli (Supplemental Figure 1).

3.3 Multiple Regression Analysis

Four subscales of the UPPS-P Impulsivity Scale (excepting positive urgency) were included simultaneously as predictors in a multiple regression model with percent

signal change units from the activated cluster of the left caudate (alcohol > pleasant

contrast) as the dependent variable. For zero-order correlations between scores on

each of the five UPPS facets and caudate activity see Table 1. Outlier detection was

based on leverage (Cohen, Cohen, West, and Aiken, 2003). One case met this criterion

and was removed.

Results indicated that negative urgency was positively associated with greater

alcohol-specific left caudate activation (Figure 2; β = .35, t(33) = 2.08, p = .045). Lack of

premeditation (β = -.32, t(33) = -1.59, p = .12), lack of perseverance (β = .21, t(33) =

1.03, p = .31), and sensation-seeking (β = .16, t(33) = 0.97, p = .34) all simultaneously

failed to significantly correlate with caudate activation. Removing participants who had

not consumed alcohol in the past year, reduced the association between negative

urgency and caudate reactivity to a statistical trend, β = .37, t(24) = 1.91, p = .068.

Positive urgency, with identical covariates, was unassociated with alcohol-specific

caudate activity, β = .13, t(34) = 0.77, p = .45.

Figure 2. Positive correlation between left caudate nucleus activation (in percent

signal change units; alcohol > pleasant contrast) and negative urgency.
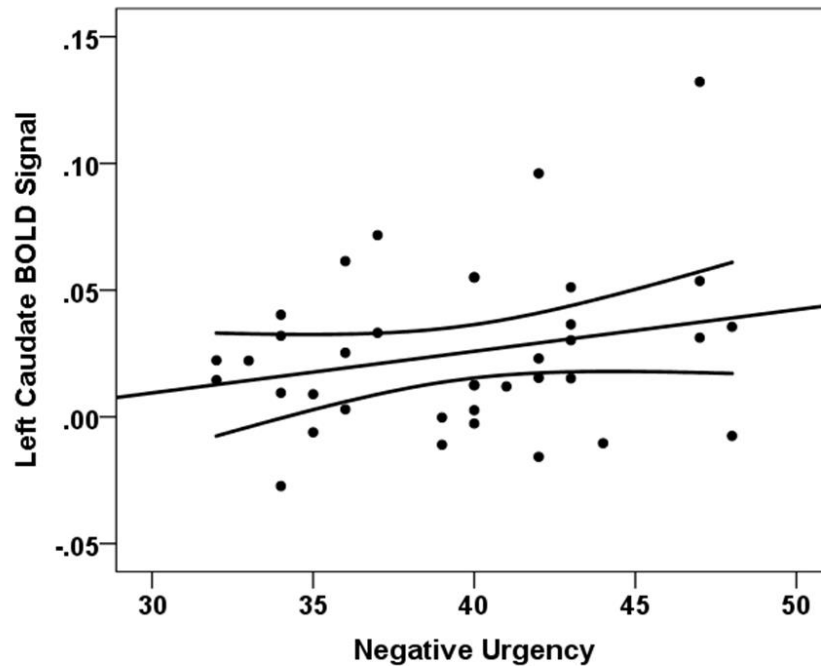
4. Discussion

Previous research has shown that negative urgency is uniquely correlated with alcohol abuse. Yet the neural and psychological mechanisms underlying this relationship remain to be fully understood. The present study assessed whether negative urgency was associated with (A) increases in alcohol cue reactivity in the striatum, (B) decreases in prefrontal reactivity or (C) both. Supporting the first hypothesis, negative urgency (while controlling for other facets of impulsivity) was associated with increases in activation of the left caudate nucleus when individuals viewed images of alcohol (as compared to pleasant images). These findings suggest that negative urgency may predict alcohol abuse by amplifying caudate reactivity and not by reducing prefrontal responses. However, we were unable to assess whether negative urgency correlated with alcohol-specific activation of the DLPFC as this brain region was not reactive to our alcohol cues.

These findings add nuance to mechanistic explanations of negative urgency's association with substance abuse (e.g., Wilbertz et al., 2014). The association between urgency and the caudate imply that bottom-up impulses are crucial determinants of the impulsive behavior of individuals high in negative urgency. It is important to emphasize the correlational nature of these data and thus directionality of our effects is impossible to establish. It may be that greater caudate reactivity to alcohol cues is an underlying factor contributing to the development of negative urgency (as suggested by Cyders et al., 2014). Longitudinal and brain stimulation approaches may allow us to establish the directionality of this effect. Additionally, negative urgency reflects impulsive responses to negative affect and yet we did not induce negative affect in this study. As such, our findings may arise from a general, tonic experience of negative affect among this population and should be explored in the context of negative affect inductions.

This experiment was limited in that our alcohol stimuli were images and not actual objects that participants could consume. Future research could provide participants with alcohol while functional neural data were acquired, further elucidating whether negative urgency functions only on the anticipated reward of alcohol or the actual pleasure of consuming alcohol. Also, the three alcohol blocks were contrasted against the larger set of nine pleasant blocks, yielding a large power differential. Alcohol and pleasant images were also not equated on pleasantness or other criteria and thus our conditions may have differed along other criteria that may have affected our results. We also did not obtain subjective reports of craving for our alcohol stimuli and thus we are unable to determine the extent to which our sample perceived them as appetitive. Further, reverse inference issues prevent us from knowing with any certainty whether

the caudate activity we observed represented craving for alcohol. In addition, our

sample population consisted of undergraduate students who were not heavy drinkers.

Thus, our sample may not have truly experienced alcohol 'cravings.' Further,

approximately 24% of our sample were non-drinkers and it is thus difficult to interpret

whether they might experience cravings for the alcohol stimuli and whether this was

reflected in the caudate.

4.1 Conclusions

The association between negative urgency and alcohol abuse may arise from an

increase in caudate reactivity to alcohol, not an insufficient prefrontal response. Our

experiment represents a key step forward into understanding the mechanisms through

which negative urgency promotes alcohol abuse. If individuals high in negative urgency

exhibit greater caudate-mediated alcohol craving, this would allow for the development

of interventions targeted specifically at this psychological process before it manifests as

alcohol dependence.

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1. Supplemental Materials

1.1 Participant Exclusion Criteria

For safety reasons, participants were excluded from our study if they reported any history of claustrophobia, seizures, head trauma, or an injury involving a metallic object. Additionally, participants were excluded if they reported a body-mass-index greater than 30 (as individuals exceeding this cutoff might be uncomfortable in the confined MRI scanner), pregnancy or suspected pregnancy, color blindness, psychoactive medication use, or psychological/neurological pathology.

1.2 fMRI Data Acquisition

All images were collected on a 3T Siemens MAGNETOM Trio scanner. Functional images were acquired with a T2*-weighted gradient echo sequence with the following parameters: 2.5s repetition time, 28ms echo time, 64 x 64 matrix, 224 x 224mm field of view, 40 3.5mm axial slices acquired in interleaved order. A 3D shim was applied before functional data acquisition. These parameters allowed for whole brain coverage with 3.5mm cubic voxels. A high-resolution, T1-weighted image was also acquired from each participant so that functional data could be registered to native anatomical space and then normalized to the Montreal Neurological Institute (MNI) atlas space.

1.3 fMRI Preprocessing

All preprocessing and statistical analyses were conducted using FSL [Oxford Center for Functional Magnetic Resonance Imaging (FMRIB); Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004; Woolrich et al., 2009]. Functional volumes were reconstructed from k-space using a linear time interpolation algorithm to

double the effective sampling rate, the first of which was removed to allow for signal

equilibration. Remaining functional volumes were corrected for head movement to the

median volume using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002),

corrected for slice-timing skew using temporal sinc interpolation, pre-whitened using

FILM, and smoothed with a 5-mm full-width-half-maximum Gaussian kernel. To remove

drifts within sessions, a high-pass filter with a cutoff period of 100s was applied. Non-

brain structures were stripped from functional and anatomical volumes using FSL's

Brain Extraction Tool (BET; Smith, 2002).

1.4 fMRI Data Analysis

FMRI analysis was performed using FSL's fMRI Expert Analysis Tool (FEAT

version 5.98). A fixed-effects analysis modeled event-related responses for each run of

each participant. Alcohol and pleasant blocks from the cue reactivity task were modeled

as events using a canonical double-gamma hemodynamic response function with a

temporal derivative. Fixation trials were left un-modeled. The contrast of interest was

alcohol > pleasant. Functional volumes and first-level contrast images from this analysis

were first registered to corresponding structural volumes using 7 degrees of freedom,

and then spatially normalized to an MNI stereotaxic space template image using 12

degrees of freedom with FMRIB's Linear Image Registration Tool (FLIRT; Greve &

Fischl, 2009; Jenkinson et al., 2002; Jenkinson & Smith, 2001). FMRIB's Local Analysis

of Mixed Effects module (FLAME; Beckmann, Jenkinson, & Smith, 2003) was used to

perform top-level, mixed-effects analysis which created group average maps for

contrasts of interest. Z (Gaussianized T/F) statistic images were thresholded using

clusters determined by $Z > 2.3$ and a (family-wise error corrected) cluster significance

threshold of $p < .05$ in *a priori* regions-of-interest (ROI; Heller, Stanley, Yekutieli, Rubin,

& Benjamini, 2006; Worsley, 2001). Whole brain analyses are displayed in

Supplemental Figure 1.

Supplemental Figure 1. Whole brain results from the Alcohol > Pleasant contrast

(Z ranges from 2.30 to 7.04).
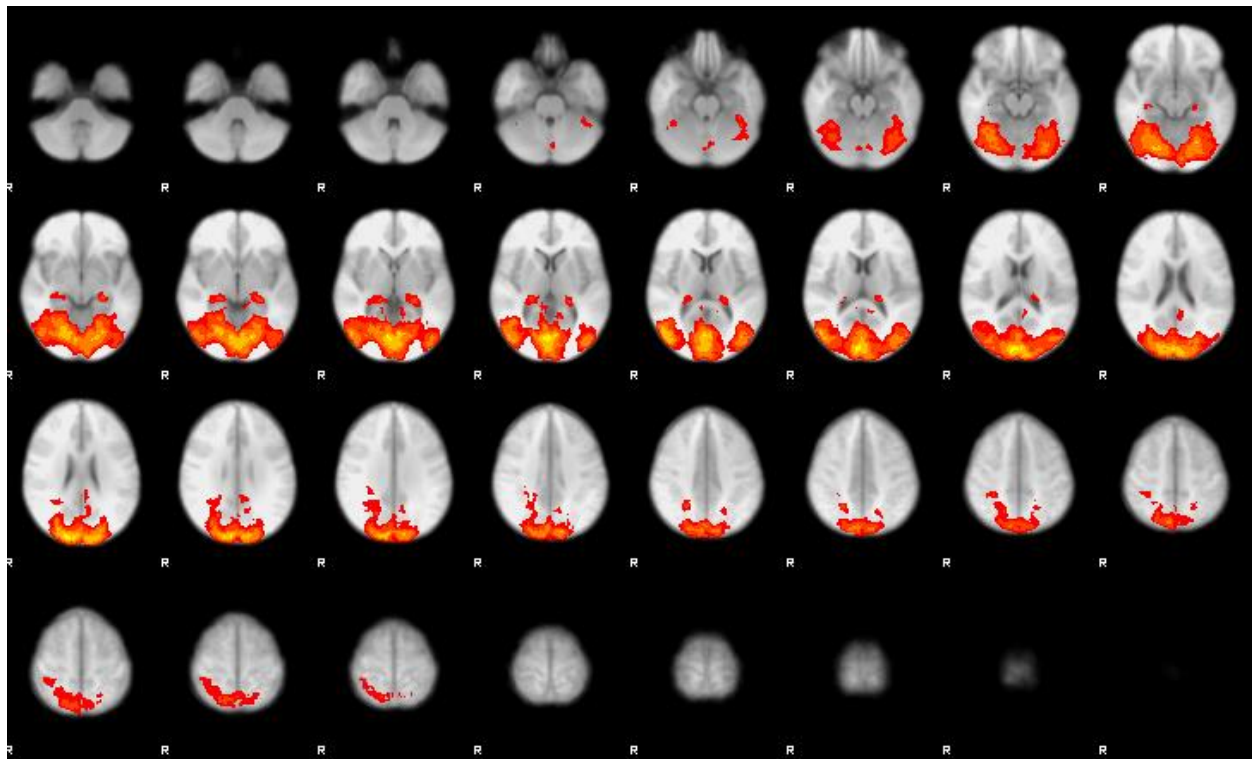
1.5 Construction of Regions-of-Interest

Region-of-interest (ROI) masks were utilized to separately constrain fMRI

analysis and multiple comparisons correction to ROIs in both hemispheres of the

caudate nucleus and DLPFC. The caudate mask was acquired from the Wake Forest

University PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003). DLPFC masks were

acquired from the Automated Anatomical Atlas, utilizing the lateral portion of the middle

frontal gyrus (Tzourio-Mazoyer et al., 2009).

Supplemental Table 1. Descriptive statistics for the five UPPS-P Impulsivity subscales.

	Observed Range	Possible Range	Mean	*SD*
Negative Urgency	28-48	12-48	39.29	4.95
(Lack of) Perseverance	24-40	10-40	32.63	4.81
Positive Urgency	39-56	14-56	50.47	4.25
(Lack of) Premeditation	24-44	11-44	35.16	5.42
Sensation-Seeking	12-39	12-48	25.47	7.24