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Jumping the Gun: Mapping Neural Correlates of Waiting Impulsivity and Relevance Across Alcohol Misuse

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ABSTRACT

BACKGROUND: Why do we jump the gun or speak out of turn? Waiting impulsivity has a preclinical basis as a predictor for the development of addiction. Here, we mapped the intrinsic neural correlates of waiting and dissociated it from stopping, both fundamental mechanisms of behavioral control.

METHODS: We used a recently developed translational task to assess premature responding and assess response inhibition using the stop signal task. We mapped the neural correlates in 55 healthy volunteers using a novel multi-echo resting-state functional magnetic resonance imaging sequence and analysis, which robustly boosts signal-to-noise ratio. We further assessed 32 young binge drinkers and 36 abstinent subjects with alcohol use disorders.

RESULTS: Connectivity of limbic and motor cortical and striatal nodes mapped onto a mesial-lateral axis of the subthalamic nucleus. Waiting impulsivity was associated with lower connectivity of the subthalamic nucleus with ventral striatum and subgenual cingulate, regions similarly implicated in rodent lesion studies. This network was dissociable from fast reactive stopping involving hyperdirect connections of the pre-supplementary area and subthalamic nucleus. We further showed that binge drinkers, like those with alcohol use disorders, had elevated premature responding and emphasized the relevance of this subthalamic network across alcohol misuse. Using machine learning techniques we showed that subthalamic connectivity differentiates binge drinkers and individuals with alcohol use disorders from healthy volunteers.

CONCLUSIONS: We highlight the translational and clinical relevance of dissociable functional systems of cortical, striatal, and hyperdirect connections with the subthalamic nucleus in modulating waiting and stopping and their importance across dimensions of alcohol misuse.

Keywords: Addiction, Binge drinking, Connectivity, Impulsivity, Machine learning, Subthalamic nucleus

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Why do we jump the gun, speak out of turn, or run a red light? Waiting and stopping are fundamental mechanisms of behavioral control. The tendency toward rapid unplanned reactions without adequate forethought broadly defines impulsivity (1). Converging preclinical and clinical evidence suggests impulsivity to be a heterogeneous construct of differing subtypes, with distinct but overlapping neural substrates (1–3). The propensity for impulsivity varies across individuals and may contribute to everyday suboptimal behaviors such as overeating and poor financial management. This ability to control impulsive behavior is impaired across a range of neuropsychiatric disorders including disorders of addiction.

Here, we explore this phenomenon in three studies. The first characterizes the neural correlates of waiting impulsivity, or anticipatory premature responding before target onset, in healthy volunteers (HV). The second and third studies assess waiting impulsivity in binge drinkers (BD) and examine the same neural correlates across social drinkers, binge drinkers, and alcohol use disorders (AUDs), respectively. This form of impulsivity is well characterized in rodents through the 5-choice serial reaction time task (5-CSRT) (4) and has important preclinical evidence supporting its role as a predictor for the development of disorders of addiction (5–7). High premorbid premature responding in rodents predicts greater nicotine use (6) and greater addiction-like behavior to cocaine (5). Mice acutely exposed to alcohol (8) in the early stages of alcohol abstinence (9) and with greater preference for alcohol (10) all exhibit enhanced premature responding. Using a novel translational task, the human 4-choice serial reaction time task (4-CSRT), which was designed with high fidelity to the rodent 5-CSRT (11,12), we have previously shown that premature responding is enhanced across individuals with alcohol and methamphetamine dependence and is elevated in smokers and recreational cannabis users (11). While the apparent transdiagnostic relevance of premature responding is clear, the underlying neural correlates in humans are yet to be elucidated.

Work in rodents has provided evidence for candidate neural regions for waiting impulsivity. Lesion studies have identified a specific network underlying premature responding implicating

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the nucleus accumbens (or human ventral striatum), infralimbic cortex (probably equivalent to human subgenual anterior cingulate), and subthalamic nucleus (STN). For example, nucleus accumbens lesions attenuate amphetamine-induced increases in premature responding (13). Highly impulsive rodents have lower $D_{2/3}$ nucleus accumbens receptor availability (14) and reduced nucleus accumbens core gray matter density (15). Furthermore, lesions of the rodent infralimbic cortex and the STN also enhance premature responding (16–19).

Special interest falls on the STN, a major relay structure within the indirect inhibitory pathway of striatal circuitry, which also receives hyperdirect projections directly from cortical regions (20,21). This rich convergence of cortical inputs implicates the STN as a crucial mediator of more complex control of motor and cognitive function. In humans, high-frequency deep brain stimulation (DBS) targeting the STN, in which high-frequency stimulation is delivered to targets of interest, thus modulating networks, is increasingly used for the symptomatic management of refractory obsessive-compulsive disorder (22) and is already established as highly effective for symptomatic management of Parkinson's disease. DBS provides insight into the STNs role and can serve as a model for STN neuromodulation and impulsivity. In rodents, increasing amplitudes of STN DBS at high frequencies increases premature responding (23). STN DBS can modulate several subtypes of impulsivity (24–26) characterized predominantly by reactive stopping with tasks involving explicit signals or enhanced responding to irrelevant stimuli or conflict. The current study focuses on premature responding or, more precisely, the capacity to wait before responding to a cue predicting reward (12).

In the first study, we examined the neural correlates of waiting impulsivity in healthy volunteers using the novel 4-CSRT and further differentiated that network from another underlying a well-characterized form of motor impulsivity, measured using the stop-signal task. With the stop-signal task, both rodent and human studies showed that action cancellation of a prepotent ongoing motor response (motor response inhibition) is dissociable from premature responding (11,27). Converging studies on stopping behaviors implicate hyperdirect connections to the STN, including from the pre-supplementary motor area (pre-SMA) and right inferior frontal cortex, as well as the indirect pathway output of the dorsomedial striatum (caudate) (3,28,29). To examine the intrinsic neural correlates of waiting and stopping, we used resting-state functional magnetic resonance imaging (fMRI) sequence and multi-echo independent components analysis, which has been shown to have up to fourfold enhancements in signal-to-noise ratio relative to single-echo fMRI scans (30), thus enabling high-fidelity assessment of small subcortical structures like STN in terms of parcellation and interregional connectivity. Based on preclinical data, we hypothesized that greater waiting impulsivity would be associated with decreased connectivity of the STN with the ventral striatum and subgenual cingulate cortex. To dissociate waiting impulsivity from motor response inhibition, we further hypothesized that impaired response inhibition as measured with the stop-signal task would be associated with lower hyperdirect connectivity of the pre-SMA and right inferior frontal cortex with STN.

We further extended a translational focus investigating premature responding in binge drinkers in the second study and examined the currently implicated neural correlates of premature responding across social drinkers, binge drinkers, and those with alcohol use disorders in the third study. We have previously shown that AUDs have elevated premature responding, tested using the 4-CSRT (11). As young adult binge drinkers are at elevated risk for developing AUD (31), we hypothesized in the second study that binge drinkers, similar to those with AUD, would have elevated waiting impulsivity. In the third study, we examined the neural correlates of waiting impulsivity, expecting that both binge drinkers and those with AUD would have decreased intrinsic connectivity of the described network. On an exploratory basis, using machine learning classification, we assessed the extent to which STN network connectivity would allow for classification of pathological drinkers from healthy volunteers.

METHODS AND MATERIALS

Participants

Subjects were scanned with a resting-state sequence. Healthy volunteers completed two behavioral tasks outside the scanner (offline). Supplement 1 includes all subject characteristics. Baseline functional connectivity of the STN with cortical and striatal regions was assessed in 66 HV. The neural correlates of waiting and motor impulsivity were examined in 55 HV, who completed both behavioral tasks along with imaging.

The recruitment strategy for HV and pathological drinkers (BD and AUD) has been previously reported (11). For the second study, we examined behavioral impulsivity in 32 BD compared with 64 age- and gender-matched HV (19 HV overlapped with the 55 HV who completed both behavioral tasks along with imaging). In the third study, STN connectivity maps of 36 abstinent subjects with AUD and 32 BD who underwent scanning were compared with matched HV. Age-matched HV were separately tested for each patient group (for AUD, 34 HVs; for BD, 32 HVs). Finally, data from a proportion of the HV (social drinkers, $n = 38$) and binge drinkers ($n = 32$) who completed the scanning and the Alcohol Use Disorders Test (AUDIT) (32) were examined.

The diagnostic and screening criteria are reported in Supplement 1. Of the AUD group, we have previously reported elevated premature responding (11), elevated delay discounting and impaired motor response inhibition (33), elevated risk seeking to likely but small rewards (34), and a shift from habitual to goal-directed learning strategies with abstinence (35).

Tasks

Premature Responding. The 4-CSRT task (Figure 1) was developed based on the rodent 5-CSRT. When four boxes appeared on the screen, subjects held down the space bar on the keyboard with their dominant index finger, indicating the cue onset time. After a specified period (cue-target interval), a green circle target appeared briefly and randomly in one of the four boxes. Subjects released the space bar and touched the box in which the target appeared. Premature responding was defined as early release of the space bar before target onset. Supplement 1 includes further task details.