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Neurobiological correlates of impulsivity in healthy adults: Lower prefrontal gray matter volume and spontaneous eye-blink rate but greater resting-state functional connectivity in basal ganglia-thalamo-cortical circuitry

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ABSTRACT

Studies consistently implicate aberrance of the brain's reward-processing and decision-making networks in disorders featuring high levels of impulsivity, such as attention-deficit hyperactivity disorder, substance use disorder, and psychopathy. However, less is known about the neurobiological determinants of individual differences in impulsivity in the general population. In this study of 105 healthy adults, we examined relationships between impulsivity and three neurobiological metrics – gray matter volume, resting-state functional connectivity, and spontaneous eye-blink rate, a physiological indicator of central dopaminergic activity. Impulsivity was measured both by performance on a task of behavioral inhibition (go/no-go task) and by self-ratings of attentional, motor, and non-planning impulsivity using the Barratt Impulsiveness Scale (BIS-11). Overall, we found that less gray matter in medial orbitofrontal cortex and paracingulate gyrus, greater resting-state functional connectivity between nodes of the basal ganglia-thalamo-cortical network, and lower spontaneous eye-blink rate were associated with greater impulsivity. Specifically, less prefrontal gray matter was associated with higher BIS-11 motor and non-planning impulsivity scores, but was not related to task performance; greater correlated resting-state functional connectivity between the basal ganglia and thalamus, motor cortices, and prefrontal cortex was associated with worse no-go trial accuracy on the task and with higher BIS-11 motor impulsivity scores; lower spontaneous eye-blink rate was associated with worse no-go trial accuracy and with higher BIS-11 motor impulsivity scores. These data provide evidence that individual differences in impulsivity in the general population are related to variability in multiple neurobiological metrics in the brain's reward-processing and decision-making networks.

Introduction

Impulsivity is a multidimensional trait defined most generally by a propensity for maladaptive decision-making, and is comprised of several related but distinct neurocognitive deficits including a lack of inhibitory control, an inability to wait and adequately plan behavior, and outsized preference for smaller, immediate rewards over larger, delayed rewards (De Wit, 2009). Excessive levels of impulsivity are a prominent feature of numerous clinical disorders, including attention-deficit/hyperactivity disorder (ADHD), substance abuse disorder (SUD), and psychopathy. In the general population, high levels of impulsivity have been linked to poorer life outcomes such as lower levels of academic success (Duckworth and Seligman, 2005) and increased propensity for substance abuse (Kreek et al., 2005). Given the important impact that impulsivity has on both personal and societal well-being, it is of interest to elucidate the neurobiological substrates that contribute to individual differences in impulsivity.

Studies consistently implicate aberrance of the brain's reward-processing and decision-making networks in disorders featuring excessive impulsivity. These networks consist of gray matter nodes in the

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ventral midbrain, basal ganglia, thalamus, motor cortices and prefrontal cortex, structural and functional connections between these nodes via basal ganglia-thalamo-cortical circuitry, and the neurotransmitter systems that innervate this circuitry. An increasing number of studies that have examined healthy samples have also linked individual differences in impulsivity to variation in these neurobiological metrics. Several studies have found that self-reported trait measures of impulsivity, such as score on the Barratt Impulsiveness Scale (BIS-11), are negatively correlated with prefrontal gray matter (Matsuo et al., 2009; Schilling et al., 2012; Holmes et al., 2016) (but see Bjork et al., 2009; Cho et al., 2013). A few recent studies in healthy adults have also found evidence for relationships between impulsivity and resting-state functional connectivity (RSFC), which measures the degree of correlated neural activity between different brain regions while the brain is at rest and is thought to reflect the strength of functional connections. These studies have examined associations between RSFC and self-reported impulsivity (Angelides et al., 2017), delay discounting (Li et al., 2013), and whether changes in RSFC and impulsivity co-occur in response to pharmacological dopamine challenges (Kayser et al., 2012; Cole et al., 2013). In one such study, up-regulation of dopamine levels via tolcapone resulted in a co-occurrence of decreased RSFC between the ventral putamen and pregenual cingulate cortex and decreased delay-discounting (Kayser et al., 2012). In addition, a sizeable literature has found associations in healthy adults between impulsivity and the activity of neurotransmitters such as dopamine. Administration of stimulant drugs such as d-amphetamine, which increase extracellular levels of striatal dopamine (Daberkow et al., 2013), has been associated with improved motor inhibition on the stop-signal and go/no-go tasks and with decreased delay discounting in healthy adults (de Wit et al., 2002). The availability of striatal D_2/D_3 dopamine receptors in positron emission tomography (PET) studies has also been associated with impulsivity in healthy adults (Lee et al., 2009; Ghahremani et al., 2012; Robertson et al., 2015). Several studies have also examined dopaminergic functioning in relation to impulsivity via spontaneous eye-blink rate (sEBR), which convergent evidence from several lines of research suggests may provide a physiological indicator of dopaminergic functioning (Karson et al., 1982, 1984; Karson, 1988; Elsworth et al., 1991; Lawrence and Redmond, 1991; Kleven and Koek, 1996; Taylor et al., 1999; Jutkiewicz and Bergman, 2004; Kaminer et al., 2011; Cavanagh et al., 2014; Groman et al., 2014a). These studies suggest a positive relationship between sEBR and dopaminergic functioning; for instance, pharmacological studies in both animals and healthy humans show that dopamine agonists increase sEBR while dopamine antagonists decrease sEBR (Elsworth et al., 1991; Taylor et al., 1999; Jutkiewicz and Bergman, 2004; Kaminer et al., 2011; Cavanagh et al., 2014), and sEBR has been found to be lower in patients with Parkinson's disease, which is characterized by low dopamine levels (Karson et al., 1984). However, despite generally consistent relationships with dopaminergic functioning, the relationship of sEBR to impulsivity has been mixed. One study found that higher sEBR was associated with poorer inhibitory control on a stop-signal task (Colzato et al., 2009), while another found that individuals with high self-ratings of disinhibition and low sEBR showed greater delay discounting; this study found no relationships between sEBR and the BIS subscales (Byrne et al., 2016).

The current study aims to advance this literature by providing a holistic account of impulsivity's relationship to multiple neurobiological metrics in the brain's reward-processing and decision-making networks in healthy adults. We present the first multi-modal dataset to simultaneously examine gray matter volume and resting-state functional connectivity in relation to impulsivity in a healthy sample. We also examine the relationship between impulsivity and spontaneous eye-blink rate to glean possible relationships with dopaminergic activity. Furthermore, we examine each of these neurobiological metrics with respect to both trait-based and task-based measures of impulsivity. The prior literature in healthy adults led us to hypothesize a negative relationship between impulsivity and prefrontal gray matter, though hypotheses for the RSFC and sEBR relationships were non-directional due to a lack of consistent findings on these metrics in prior literature.

Materials and methods

Overview

This study of n = 105 healthy adults examines relationships between impulsivity and gray matter volume, resting-state functional connectivity, and spontaneous eye-blink rate (sEBR), a peripheral measure of central dopaminergic activity. Impulsivity was measured both by self-rating of impulsivity using the Barratt Impulsiveness Scale (BIS-11) and by performance on a go/no-task. Since impulsivity is a multi-dimensional construct encapsulating a number of distinct cognitive processes, we evaluated the neurobiological metrics with respect to multiple metrics from the BIS-11 and go/no-go task that captured this range of impulsivity subdomains. On the BIS-11, we measured attentional, motor and non-planning impulsivity subscale scores in addition to total score; on the task, we measured accuracy on no-go trials to gauge the capacity to withhold prepotent responses, and post-error slowdown to measure the tendency to proceed more deliberately after negative feedback.

First, whole-brain voxel-wise analyses were used to examine relationships between GMV and the impulsivity metrics. Next, we examined the relationship between RSFC and the impulsivity metrics using seed-to-whole-brain analyses; in order to assess RSFC in different networks in the basal-ganglia-thalamo-cortical circuitry, we used six a priori basal ganglia seeds (Di Martino et al., 2008) that have been shown to participate in functionally distinct networks, in addition to a substantia nigra seed (Tomasi and Volkow, 2012a) and ventral tegmental area seed (Tomasi and Volkow, 2012a) to assess RSFC in distinct dopaminergic pathways. Lastly, we examined correlations between sEBR and the impulsivity metrics. Age and sex were used as covariates in all analyses. Additionally, all volumetric analyses also included intracranial volume as a covariate.

Participants

127 healthy adults were recruited from the community for a study on health and well-being through internet and local newspaper advertisements. Participants provided written informed consent for study procedures that were approved by the UW-Madison Health Sciences Internal Review Board. Criteria for exclusion included use of psychotropic or steroid drugs, night-shift work, diabetes, peripheral vascular disease or other diseases affecting circulation, pregnancy, and current smoking habit or alcohol or drug dependency; exclusion criteria were assessed via self-report. Structural magnetic resonance imaging (MRI) scans were obtained for 106 subjects; one subject's scan was excluded due to poor image registration. Thus, data from a total of 105 subjects [age, 48.6 ± 10.9 years (mean ± SD); 65 women, 40 men] were included in the gray matter volume analyses. 27 of these 105 subjects were excluded from RSFC analyses due to excessive motion during the functional MRI scan, and so data from 78 subjects were used in the RSFC analyses [age, 48.9 ± 11.0 (mean ± SD); 50 women, 28 men]. Spontaneous eye blink rate (sEBR) data was obtained for 98 of these 105 subjects, and so analyses involving sEBR included data from 98 subjects [age, 48.9 ± 10.8 years (mean ± SD); 58 women, 40 men].

Barratt Impulsiveness Scale (BIS-11)

The BIS-11 (Patton and Stanford, 1995) is a self-report questionnaire containing 30 questions, each of which requires the subject to choose between ‘Rarely/Never’, ‘Occasionally’, ‘Often’ and ‘Almost