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INTRINSIC ACTIVITY

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MEETING ABSTRACT

A2.2

Multiplexing motor functions and impulsive traits is molecularly dissociated by subthalamic metabotropic glutamate receptor 4

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Background: Inhibitory control, the ability to suppress and cancel prepotent responses is a key element of cognitive control. The balance between action and behavioral inhibition is biased by impulsivity, a highly complex behavior, involving incentive salience, attention and fast action response. Maladaptive inhibitory control is highly correlated with increased trait impulsivity. Impairment in this function underlies both impulsive and compulsive behaviours, which are key traits of conditions such as attention deficit / hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), as well as addiction. Despite its ethological and clinical significance, neuronal mechanisms specifically controlling impulsive responding remain largely unknown. We set out to screen for brain regions and potential molecular targets dissociating impulsivity from motor control using a well-established behavioral task along with functional imaging and specific brain-region manipulations.
Methods: We combined the Go/No-Go task (GNG) with an unbiased brain-wide scan using functional imaging (fMRI) to identify brain regions associated with naturally occurring trait impulsivity variations within a mouse population. Next, we conducted a set of optogenetic and pharmacological manipulations along with RNA silencing in order to identify brain regions modulating trait impulsivity and to pinpoint a potential molecular target.
Results: We were able to identify the subthalamic nucleus (STN), a node of the basal ganglia circuitry primarily linked to general motor control, as a hotspot for trait impulsivity via fMRI. Its optogenetic inhibition in GNG task increased impulsivity. Furthermore, administering a positive allosteric modulator of the metabotropic glutamate receptor 4 (mGluR4), a molecule thought to decrease STN firing, we were able to phenocopy our optogenetic observations. Using our fMRI approach in combination with the pharmacological treatment we were able to show that the cross-point of mGluR4 activity and impulsivity is indeed the STN. Conversely, shRNAi-mediated knocking down of STN mGluR4 reduced impulsivity in our task. Importantly, none of our manipulations affect general motor behavior.
Discussion: Based on our findings we conclude that the STN is not only a switch for motor activity but that at a more discrete activity level it modulates trait impulsivity. Additionally we identify the mGluR4 as the point of dissociation for STN functionality, rendering it a potential novel biomedical target at the crossroad between motor and cognitive functions.

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