Mapping Trait Impulsivity Networks: Resting-State fMRI, Pharmacological Modulation, and Genetic Targets

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1 Introduction

Impulsivity is a possible behavioral endophenotype and an important transdiagnostic feature that can be linked to a variety of psychiatric conditions, such as ADHD, personality disorders, and substance use disorders. Yet the neural and molecular network circuitry underlying natural variation in trait impulsivity remains understudied. Here, we employ a multimodal approach combining neuroimaging and transcriptomic data to map the functional and molecular architecture of trait impulsivity in the mouse brain. Piszczek et al. (2022) identified the subthalamic nucleus (STN) as a key neural correlate of trait impulsivity. Extending this work, we focus not on a single brain region but on networks of interacting brain regions associated with impulsivity. In addition, we probed pharmacological modulation to broaden the phenotypic expression of impulsivity and to identify potential pharmacological targets. To alter impulsivity-related networks in the mouse brain, we used amphetamine, a dopaminergic agonist and psychoactive stimulant with high abuse potential, as well as atomoxetine, a noradrenergic reuptake inhibitor that is indicated for the treatment of ADHD. Both drugs have been shown to alter impulsive behavior in humans and mice and to operate on distinct neuroanatomical substrates (Broos et al., 2012).

2 Methods

Isogenic C57Bl/6J mice were behaviorally assessed for their level of impulsivity using a Go/No-Go task, a well-validated assay of impulse control in both humans and rodents. Based on their precue response rate and No-Go performance, mice were split into groups of high and low impulsivity phenotypes. To measure intrinsic functional connectivity patterns, resting-state fMRI was performed on both groups. Prior to imaging, animals were acutely administered amphetamine, atomoxetine, or saline (control condition) before anesthesia. Transcriptomic data are obtained from publicly available sources such as the Allen Brain Atlas (https://brain-map.org).

3 Analysis

Based on experimental manipulation, we set multiple group contrasts covering trait comparisons (high vs. low impulsivity), drug comparisons (e.g., amphetamine vs. atomoxetine), and trait-by-drug interactions (e.g., high-impulsivity amphetamine vs. high-impulsivity atomoxetine). Network-based statistics have been computed to identify significant subnetworks of connected edges that show altered connectivity between the experimental groups. First, we perform an fMRI network analysis and, based on graph theoretical centrality measurements, nominate brain network hubs associated with group differences. Second, to reductionistically link functional connectivity patterns with molecular substrates, an exploratory gene set enrichment analysis is performed for the selected brain regions (Freus et al., 2025). Genes enriched in regions corresponding to the identified hubs are benchmarked against genes known to be involved in the mechanisms of action of amphetamine and atomoxetine, as well as candidate genes from GWAS studies on impulsivity.

4 Outlook

This approach nominates specific brain regions, their network structures, and candidate genes potentially underlying individual variation in impulse control and its pharmacological modulation. Thus, it provides a multimodal perspective on the neurobiology of impulsivity with implications for understanding disease vulnerability and therapeutic target discovery.

References

Broos, N., Schmaal, L., Wiskerke, J., Kostelijk, L., Lam, T., Stoop, N., Weierink, L., Ham, J., De Geus, E. J. C., Schoffelmeer, A. N. M., Van Den Brink, W., Veltman, D. J., De Vries, T. J., Pattij, T. and Goudriaan, A. E. (2012). The Relationship between Impulsive Choice and Impulsive Action: A Cross-Species Translational Study. *PLoS ONE*, 7(5):e36781.

Freus, N. K., Wank, I., Häfele, M., Kalinichenko, L. S., Müller, C. P., Strobelt, S., Ludwig, A., Hess, A. and Kreitz, S. (2025). Pharmacological and resting state fMRI reveal Osteocalcin's effects on mouse brain regions with high Gpr37 and Gpr158 expression. *Scientific Reports*, 15:10116.

Piszczek, L., Constantinescu, A., Kargl, D., Lazovic, J., Pekcec, A., Nicholson, J. R. and Haubensak, W. (2022). Dissociation of impulsive traits by subthalamic metabotropic glutamate receptor 4. *eLife*, 11:e62123.