We are amid an opioid epidemic and despite access to evidence-based treatments, individuals with opioid use disorder (OUD) continue to reuse drugs and relapse (Blum et al., 2018). Therefore, identifying mechanisms that perpetuate risky drug use is of utter importance. One potential mechanism may be how individuals with OUD make decisions. Recent evidence suggests that individuals with OUD have higher tolerance for known and unknown risks compared to healthy controls, and that increased tolerance of unknown risk is predictive of future drug use in patients with OUD (Chen et al., 2020; Konova et al., 2020). Additionally, there is evidence supporting changes in functional connectivity between value-encoding regions in the brain (e.g., ventromedial prefrontal cortex and ventral striatum) and other regions of the brain (Li et al., 2013; Tolomeo & Yu, 2022). However, how these changes in functional connectivity give rise to changes in decision-making, and subsequently future drug use, is not well understood. Thus, understanding how these regions interact with each other, and other regions in the brain, may offer key insights into how changes in decision-making may result in future drug use. In the current study, I aimed to study the differences in functional resting-state connectivity between patients with OUD and healthy controls and apply graph to identify a potential neural target for future interventions.

Here, we collected eight-minute resting state scans from 29 patients with OUD (Mage=45.4, SEage=2.06, 26 % female) and 21 controls (Mage=47.31, SEage=2.71, 37% female). Resting state data was collected as part of a larger study examining risk tolerance in patients with OUD. Functional scans were preprocessed with fMRIPrep 1.5.4 [ (Esteban, 693Markiewicz, et al. (2018); Esteban, Blair, et al. (2018), which is based on Nipype 6941.3.1 (Gorgolewski et al. (2011); Gorgolewski et al. (2018)]. Preprocessed resting-state data was subsequently smoothed with a 6mm smoothing kernel in SPM. In the current study, I focused on 15 regions of interests as these regions are reported to be associated with decision-making and drug addiction. These regions included the amygdala, ventral striatum, dorsolateral prefrontal cortex, orbitofrontal cortex, thalamus, inferior frontal gyrus, anterior cingulate cortex, midbrain, and ventromedial prefrontal cortex. I calculated partial correlations between each region of interest while controlling for nuisance variables (obtained from fMRIPrep): motion regressors, white matter, and cerebral spinal fluid. These partial correlation coefficients were then converted to Fisher's Z to approximate a normal distribution.

After generating the correlation matrices, I attempted using several toolboxes in MATLAB to apply graph theory to my resting state analyses: the Brain Connectivity toolbox (Li et al., 2013), GRETNA Toolbox (Wang et al., 2015), and CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). Between the first two toolboxes, I was left with a series of errors. After thresholding the correlation matrices, I attempted different tools within these two toolboxes to apply small world theory (given the small sample of ROIs this may have been one of the root causes, in addition to the presence of negative values). I also attempted network metrics such as degrees/degree centrality as a lower-level attempt. Following these two error prone approaches, I examined the difference in resting state differences between patients and controls, finding higher connectivity between the ventromedial prefrontal cortex and the orbitofrontal cortex in patients compared to controls. To continue my focus on applying graph theory to a subset of patients with OUD (n=14) which displayed the highest correlation values between regions of interests overall, and maintained the sample demographics (i.e., age and sex). Using the previously generated correlation matrices that were converted to Fisher's Z and thresholded for significance, using functions within MATLAB (e.g., “graph” for undirected graphs, and “degree” for node degree). I generated graphs for these 14 individuals and identified the amygdala displayed the highest node centrality across subjects (~ 13 connections). This was interesting to see the amygdala as the most central node as this region has been associated with more impulsive decisions (Gupta et al., 2011).

Determined to attempt another toolbox, I used the CONN toolbox where I Regenerated correlation matrices for the 14 subjects using the AAL atlas with 164 regions of interest. CONN also has additional denoising techniques that I applied to the data. Additionally, I computed regression models while controlling for nuisance variables. These regression models were then used to compute network level and graph level analyses. Ultimately, I found that the putamen (a substructure within the ventral striatum) was the central node for these 14 subjects.

Not surprisingly, I found resting-state differences between patients with OUD and healthy controls, particularly for the connection between the ventromedial prefrontal cortex and orbitofrontal cortex. Using the 15 ROIs, I found that amygdala was the central node in a subset of patients but after applying a larger correlation matrix, found that the putamen was actually the more central node, and the amygdala was not a part of this connection. This suggests that the ventral striatum may be an important region to consider as a target for future interventions.

**GITHUB LINK TO AND PRESENTATION SLIDES:**

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