Nicotine abstinence induced connectivity changes in amygdala and insular circuits predict relapse

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Background: Amygdala and insula are involved in affective functions that play critical roles in developing, maintaining and relapsing to drug addiction. While lesions to insula are associated with a diminished craving for smoking, nicotine withdrawal is associated with an elevated amygdala-insula rsFC circuit. We hypothesized that acute nicotine abstinence would induce rsFC changes in amygdala and insula circuits, and the resultant circuit changes would correlate with nicotine withdrawal symptoms and predict treatment outcome.

Methods: Treatment-seeking healthy smokers (n=50) participated in two imaging sessions (smoking and 24 hr abstinence). Nicotine dependence severity (FTND), withdrawal (MNWS), craving (QSU-B), and affect (PANAS) were measured at each session. Whole-brain rsFC analysis was performed with bilaterally-combined six seeds in superficial (SFA), laterobasal (LBA), centromedial amygdala (CMA), and anterior (AI), middle (MI), posterior insula (PI). The correlations between connectivity changes and behavioral measures were examined. Backward stepwise logistic regression was used to select altered amygdala and insula circuits predicting 7-day relapse. Age and FTND were entered as a baseline clinical model. Change scores during abstinence challenge (MNWS, QSU-B) were added to the clinical model to form an intermediate model. A full model was constructed by combining circuit predictors with the intermediate model.

Results: The MNWS, QSU-B, and PANAS negative scores were elevated (p<.001) during abstinence. An increase in circuit strength was seen following acute abstinence (Fig.1). Regression analysis revealed that PI-left SMC circuit positively correlated with craving, while PI-left SPL correlated with PANAS negative scores. In contrast, LBA-left PI was associated with decreased withdrawal scores. Backward stepwise regression retained the LBA-right PI circuit, and the PI-right SMC circuit, combining with FTND, as neural predictors. Specifically, relapse at 7 days was predicted by higher FTND, larger PI-SMC rsFC increase, and smaller LBA-insula rsFC increase. The predictive value of the relapse models was examined using ROC analysis. The full model produced a relatively high AUC of 83.6%, whereas the intermediate and clinical models were 73.3% and 72.9%.

Conclusions: Consistent with previous study, nicotine abstinence induced rsFC changes in both amygdala and insula circuits. The abstinence-induced increase between PI and SMC, which is positively associated with abstinence-induced craving and predict relapse to drug use, may underlie nicotine sensitization and interoceptive perception of the sensory representation of drug craving. In contrast, the increased connectivity between amygdala and PI, which is negatively correlated with withdrawal symptoms and positively associated with successful abstinence, may suggest a neural mechanism of coping with abstinence-induced withdrawal. A combination of these two circuits was able to better predict smoking relapse.