

Altered resting-state functional connectivity of the insular system in chronic cocaine users

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Introduction Drug addiction is a chronic and relapsing brain disorder characterized by compulsive drug seeking and use despite negative consequences. Accumulative evidence has indicated the involvement of the insular system in drug addiction. For example, abnormal insular structure¹ and functional activity² were found in cocaine dependents; Insular damage was found to disrupt addiction to smoking³. On the other hand, studies on healthy subjects demonstrated that the insula plays a fundamental role in interoception⁴. Based upon these findings, addiction models were proposed from the interoception perspective^{5,6}, linking the insular system and related interoceptive function to drug addiction. However, there is remarkable paucity of research addressing the relationships between the interoception, neurobiological characteristics of insula and addiction behaviors. The current study aimed to examine the resting-state functional connectivity (FC) of the insular system, and its potential relationship with abnormal behaviors in cocaine dependents.

Methods Forty-seven chronic cocaine users (CU) and 47 healthy controls (HC) matched on age, gender, IQ and education participated in the study. Toronto Alexithymia Scale (TAS-20) was used to assess the alexithymic trait, which is highly related to interoceptive function⁷. Resting-state fMRI data of 6 min was collected on each participant and processed with the following steps including slice-timing and head motion corrections, normalization, smoothing, detrending, low-pass filtering (0.1Hz), and removing of potential confounding factors by regression. Three insular seeds in each hemisphere, in the anterior, middle and posterior insula respectively, were adopted from previous study⁸ (Fig. 1). Mixed 2x2 ANOVA (hemisphere x group) analyses were employed to examine potential differences in insular FC. Relationships between TAS and addiction behaviors as well as FC were examined.

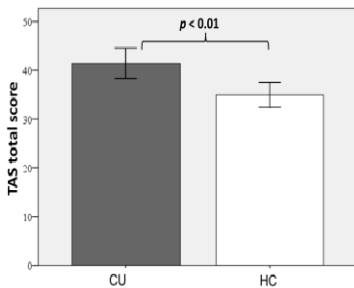


Fig.2 Difference in TAS scores between CUs and HCs.

and ACC in an fMRI study using a GO/NoGo task². Interoception, which is highly correlated with alexithymic measurement (TAS)⁷, has been suggested involving in cue-induced craving, poor perception of emotion in drug dependents^{5,6}. The elevated TAS scores reported in the current study, which is in line with a previous studies that reported elevated TAS measures in substance-addicted individuals such as alcoholics⁹, may imply alterations of emotion awareness and interoceptive function in chronic cocaine users. As suggested in the addiction models, altered relationship between the insula-ACC connectivity and TAS score may indicate re-wired/impaired neural circuitry associated with emotional and interoceptive functions in chronic drug users. In conclusion, the present study revealed altered insula-cingulate and insula-frontal functional connectivity, abnormal alexithymic trait and dis-association between insula-cingulate functional connectivity and alexithymia in chronic cocaine users. These findings may shed insight on the neurobiological bases of drug addiction.

Result Decreased FCs between ACC and the three divisions of insula were observed in CU (Fig. 1). Besides, enhanced negative FC between the right dorsal lateral prefrontal cortex and the posterior insula was found in CU. The TAS total score was significantly higher in the CU group than the HCs (Fig. 2). Positive correlation between the total score of TAS and cocaine dependence (numbers of DSM-IV criteria met) was found (Fig. 3a). In addition, score on the TAS subscale, externally oriented thinking, was found positively correlated with the cocaine current use (money spent for cocaine per week) (Fig. 3b). The functional connectivity between anterior insula and ACC was negatively correlated with TAS score only in the HC group but not in the CU group (Fig 3c).

Discussion Altered functional connectivity insular system and elevated TAS score, as well as their disrupted correlation were observed in chronic cocaine users. Decreased functional connectivity between the insula and ACC may reflect cognitive deficit depicted by hypoactivity in both insula and ACC in an fMRI study using a GO/NoGo task². Interoception, which is highly correlated with alexithymic measurement (TAS)⁷, has been suggested involving in cue-induced craving, poor perception of emotion in drug dependents^{5,6}. The elevated TAS scores reported in the current study, which is in line with a previous studies that reported elevated TAS measures in substance-addicted individuals such as alcoholics⁹, may imply alterations of emotion awareness and interoceptive function in chronic cocaine users. As suggested in the addiction models, altered relationship between the insula-ACC connectivity and TAS score may indicate re-wired/impaired neural circuitry associated with emotional and interoceptive functions in chronic drug users. In conclusion, the present study revealed altered insula-cingulate and insula-frontal functional connectivity, abnormal alexithymic trait and dis-association between insula-cingulate functional connectivity and alexithymia in chronic cocaine users. These findings may shed insight on the neurobiological bases of drug addiction.

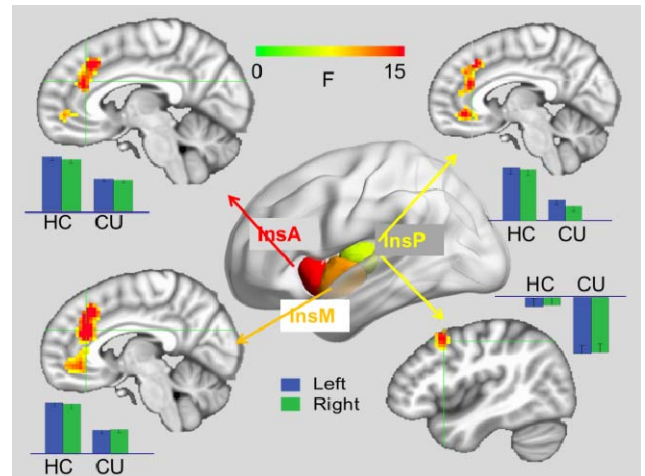


Fig.1 Insular seeds and functional connectivity differences between the CU and HC groups.

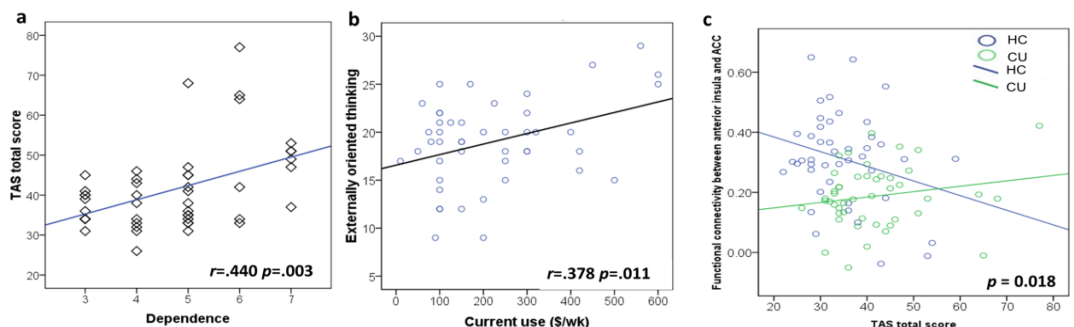


Fig. 3 Relationships between TAS, addiction behaviors and functional connectivity.

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