Disrupted network interactions in chronic cocaine dependents as revealed by modular network analysis of resting-state functional MRI

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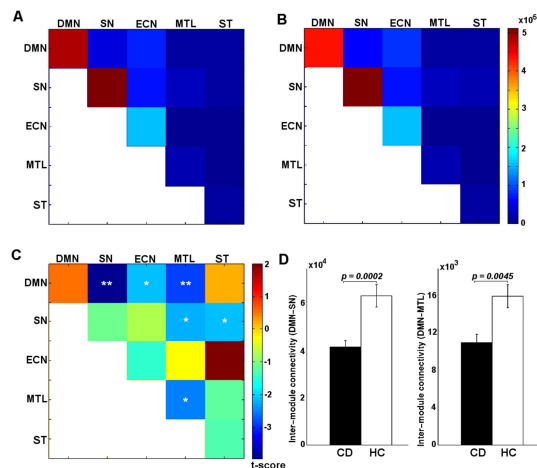
Fig 1. Intra- and inter-module connectivity for HC (A) and CD (B) groups. C, Group differences in intra- and inter-module connectivity. D, Bar plots for significant differences in inter-module connectivity between DMN and SN, and between DMN and MTL. **, $p < 0.005$; * $p < 0.05$.
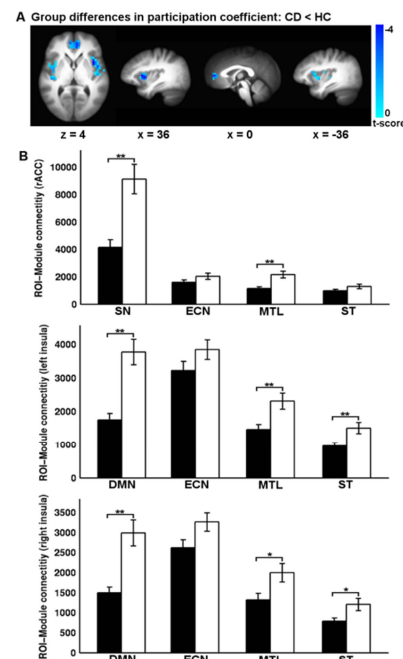
Background: Drug addiction is a neuropsychiatrc disorder characterized as compulsive drive to take the drug even at the expense of serious adverse consequences. Functional neuroimaging studies on chronic cocaine dependents revealed their impairments in various brain circuits [1], including the midbrain dopaminergic areas and their projection to the striatum (ST) regions involved in reward [2,3,4], the hippocampus and amygdala regions in medial temporal lobe (MTL) implicated in memory and emotion [2], and the executive control network (ECN) related primarily to external cognitive function [5]. In addition, two other brain networks, the default mode network (DMN) putatively involved in self-referential processes [6] and the salience network (SN) implicated in interoceptive processing [7], have also shown addiction-related impairments. However, whether and how the network-level interactions are disrupted in chronic cocaine users is unknown. Here, we used modular network analysis based on graph theory to examine the modular organization of functional brain networks and the alterations in network-level interactions following chronic use of cocaine.

Methods: 53 cocaine dependents (CD) and 52 healthy controls (HC) matched for gender and age were recruited for resting fMRI scan in this study. Following standard preprocessing, a voxel-wise brain network was formed for each subject by calculating the Pearson correlation of time courses between any pair of voxels. The resulting correlation matrix was binarized by setting the elements to 1 if their corresponding correlations were statistically significant ($q < 0.001$, FDR-corrected) and 0 otherwise. To identify the modules of interest, we performed voxel-wise modular analysis using the Infomap algorithm [8] on group networks averaged across each cohort. We then investigated cocaine-related alterations of intra-/inter-module connectivity at both module and voxel levels. At the module level, the intra-module connectivity was the sum of all connections within a module, whereas the inter-module connectivity between two modules was calculated as the sum of connections between them [9]. At the voxel level, we calculated the intra-module degree and participation coefficient (PC) for each voxel as indices of their intra- and inter-module connectivity. The within-module degree quantifies the connectedness of a voxel to other voxels in its module, whereas the PC measures the weight distribution of a node among all the modules in the network [10]. We also assessed the relationships between intra-/inter-module connectivity and cocaine-using behaviors and Toronto Alexithymia Scale (TAS-20) scores (total and sub-scale scores).

Results: In both HC and CD groups, modular analysis uncovered five modules that were of particular interest in the present study, including the DMN, SN, ECN, MTL and ST. We then examined alterations in the intra- and inter-module connectivity for all the five functional modules (Fig.1). Compared with HCs, CDs exhibited significantly decreased inter-module connectivity between the DMN and SN modules ($p = 0.0002$), and between the DMN and MTL modules ($p = 0.0045$). We also explored the cocaine-related alterations in voxel-wise intra- and inter-module connectivity. We found that, compared with HCs, CDs showed significant decreased PC in bilateral insula and rostral anterior cingulate cortex (ACC). These regions were then served as seed regions to further assess the differences in connectivity with the rest four modules (Fig.2). The rACC located within the DMN module showed decreased average connectivity with SN and MTL modules. The SN regions of bilateral insula showed decreased average connectivity with DMN, MTL and ST modules. Finally, we found that the intra-module connectivity within SN module showed significantly negative correlation with difficulty of describing feelings (DDF), which is a sub-scale score of TAS-20 (Fig.3).

Fig. 3. Relationship between DDF and intra-module connectivity in SN.

Fig. 2. Group differences in participation coefficient. A, Regions of rACC and bilateral insula showed decreased participation coefficient in CD group. B, Differences in average connectivity between the three ROIs in A and the rest four modules.
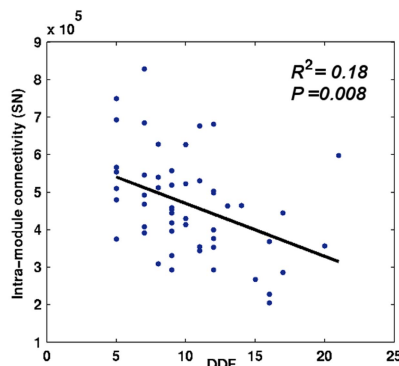
Discussion: Our results demonstrate that cocaine addiction is associated with disruptions of network-level interactions, including default mode, salience and emotional networks. The abnormal interactions between SN and DMN could be reflective of the "triple network model" [1], which focused on the significant role of the deficits of dynamics within and between ECN, SN and DMN in addiction. We also observed that the cocaine addicts with higher difficulty in describing feelings tend to be less connected within SN. This may suggest that the deficits in interoceptive function in cocaine addicts is associated with the impaired SN system, which has been shown to be involved in integrating interoceptive information [11]. Together, our results may provide novel insights into the neurobiological mechanisms of cocaine addiction.

References:

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