Disrupted modular organization and abnormal topological properties of the ACC in abstinent alcohol dependent patients to alcohol-cue reactivity

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Background: Our brain's functional system is characterized by a complex network. Recent advances of graph theory have provided a tool to study the underlying properties, such as modularity. Modules refer to subsets of nodes that are densely connected to other nodes in the same module but sparsely connected to nodes in other modules. Besides that, it also allows the location of key regions within the network, so-called hubs, depending on their contribution to intra- and inter-modularity connectivity [1]. Craving and relapse are the most problematic aspects to the treatment of alcoholism and are often triggered by alcohol-related environmental cues. In addition, previous evidence indicates that the ACC plays a predominate role in cue-induced relapse behavior [2-3]. However, up to now, the topological functional networks and role of ACC related to alcohol cues reactivity are still unknown. To address this question, we used graph theory to test the hypothesis that alcoholism is associated with abnormal modular organization and topological properties of the ACC in response to alcohol-associated cues.

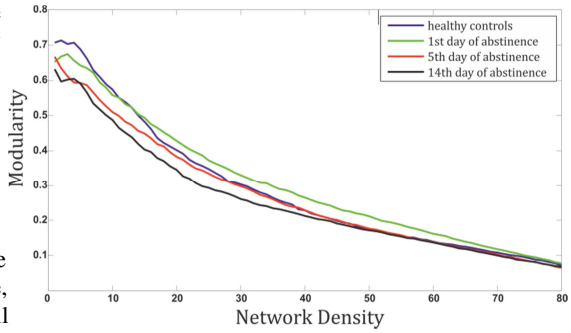

Fig. 1: The mean value of modularity

Methods: Alcohol dependent patients (N=8) were measured three times by fMRI (cue reactivity), on day 1 (acute withdrawal, D1), day 5 (D5), and day 14 (D14) of abstinence, respectively. A healthy control group (N=7) was measured twice (D1 and D14). All images were acquired using a 3T scanner (MAGNETOM TimTrio; Siemens, Erlangen, Germany). fMRI cue reactivity task was presented by a block design consisting of alternating alcoholic beverages and neutral control stimuli (pictures). Each block was presented for 4s, consisting of 5 stimuli. Data analysis was carried out using SPM8 and brain connectivity toolbox. Network properties were calculated over the range of network density from 0.01 to 0.8 with 0.01 intervals.

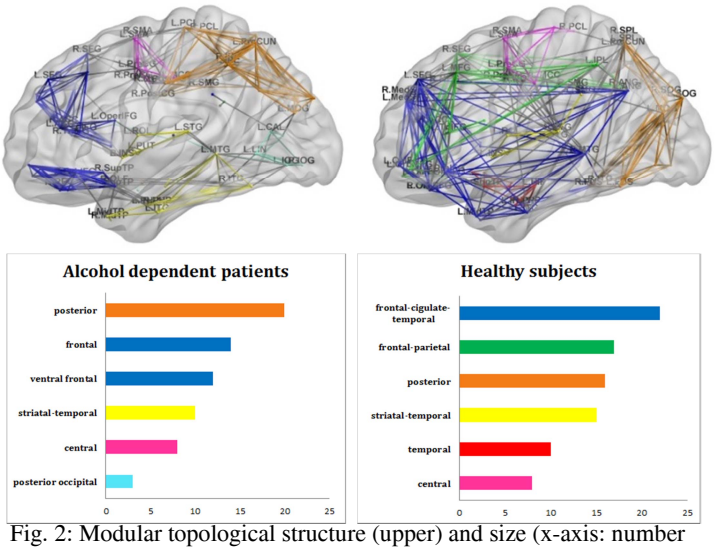

Fig. 2: Modular topological structure (upper) and size (x-axis: number of nodes) (bottom).

Results: In the patients group, repeated ANOVA analysis shows a trend towards decreased modularity over early abstinence. Similarly, alcohol dependent patients (at D14) show a trend to less modularity in contrast to healthy subjects (Fig.1). But there are clear differences in the modular size, composition and topological role profile of modules between patients (D14) and healthy subjects. In short, the regions comprising the large dorsal fronto-cingulate-temporal module of the healthy brain network have segregated into two smaller and more local modules in the alcohol dependent patients. Additionally, patients show a lack of direct inter-modular connection between dorsal-ventral frontal modules and the frontal–parietal module disappeared (Fig.2). An increase in the number of intra-modular connectivity of the ACC can be shown in alcohol dependent patients (D14) (Fig.3).

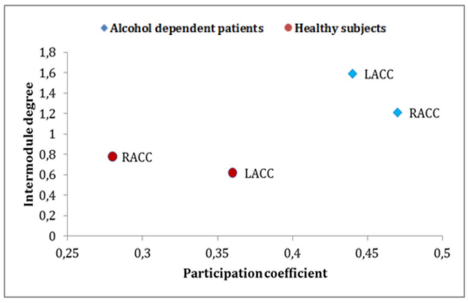

Fig. 3: Topological properties of hubs (X-axis: reflecting the inter-modular connection, Y-axis: reflecting the intra-modular connection)

Conclusions: The brain connectivity analysis for alcohol dependent patients shows a trend for less modularity, implying an increasingly disrupted modular organization over early abstinence. Additionally, patients show a lack of interconnection between dorsal and ventral frontal modular nodes suggesting a deficit in the top-down inhibition system which is closely associated with craving and alcohol seeking behavior. Moreover, the ACC is a hub in this network with abnormal activity/importance in the patients group. These observations are in line with our hypothesis.

References: [1] Bullmore ET, Bassett DS. Brain graphs: graphical models of the human brain connectome. Annu.Rev. Clin. Psychol. 2011; 7:113-140. **[2]** Grüsser SM, Wrase J, Klein S, et al. Cue-induced activation of the striatum and medial prefrontal cortex is associated with subsequent relapse in abstinent alcoholics. Psychopharmacology. 2004; 175(3):296-302. **[3]** Vollstädt-Klein S, Wichert S, Rabinstein J, et al. Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. Addiction. 2010; 105(10):1741-1749.