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Model-Free Functional Connectivity and Impulsivity Correlates of Alcohol Dependence: A Resting-State Study

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Abstract

Background—Alcohol dependence is characterized by impulsiveness toward consumption despite negative consequences. Although neuroimaging studies have implicated some regions underlying this disorder, there is little information regarding its large-scale connectivity pattern. This study investigated the within- and between-network functional connectivity (FC) in alcohol dependence and examined its relationship with clinical impulsivity measures.

Methods—Using Probabilistic Independent Component Analysis (PICA) on resting-state fMRI (rs-fMRI) data from 25 alcohol dependent (AD) and 26 healthy control (HC) participants, we compared the within- and between-network FC between AD and HC. Then, the relationship between FC and impulsiveness as measured by the Barratt Impulsiveness Scale (BIS-11), the UPPS-P Impulsive Scale and the delay-discounting task (DDT) was explored.

Results—Compared to HC, AD exhibited increased within-network FC in salience (SN), default-mode (DMN), orbitofrontal cortex (OFCN), left executive control (LECN) and amygdala-striatum (ASN) networks. Increased between-network FC was found among LECN, ASN and SN. Between-network FC correlations were significantly negative between Negative-Urgency and OFCN pairs with RECN, anterior DMN (aDMN), and posterior DMN (pDMN) in AD. DDT was significantly correlated with the between-network FC among the LECN, aDMN and SN in AD.

Conclusions—These findings add evidence to the concept of altered within-network FC and also highlight the role of between-network FC in the pathophysiology of AD. Additionally, this

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Conflict of Interest:

All authors acknowledge that there is no conflict of biomedical financial interests in performing this study or in preparing this manuscript.

Authors' contribution:

RM and XZ were responsible for the study concept, and design. RM was responsible for the acquisition of fMRI data. XZ performed the data analysis. KM and CC assisted with data analysis and interpretation of findings. XZ and CC drafted the manuscript. DD provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

study suggests differential neurobiological bases for different clinical measures of impulsivity that may be used as a systems-level biomarker for alcohol dependence severity and treatment efficacy.

Keywords

fMRI; Functional Connectivity; Resting state; Impulsivity; Alcohol dependence; ICA

Introduction

Alcohol dependence is a mental disorder with an impulsive drive toward alcohol consumption and inability to inhibit its consumption despite negative consequences. Impulsivity is a multidimensional, multifaceted characteristic and construct associated to different aspects of alcohol use, abuse, and dependence. This multidimensional aspect has generated great variability in the usage of impulsivity measures, especially on the personality traits. Despite this variability, personality assessment in addition to neuroimaging data has shown individually to have high predictability for current and future alcohol misuse. The evidence from Whelan et al. 2014, not only strengthens the potential of neuroimaging as a tool to generate intermediate endophenotypes in addiction, but also highlights the importance of combining neuroimaging and personality assessments in order to elucidate the biological mechanisms underlying addiction and can lead to the development of improved treatment strategies (Whelan et al., 2014).

The neural mechanisms in the addicted brain are complex due to the dynamic changes of different regions and their connectivity. Despite this complexity, a triadic neurocognitive model has been proposed by Noël et al. 2013 that the weakened “willpower” that characterizes most addiction behaviors is the results of the altered interaction among three systems (Noel et al., 2013): 1) Impulsive system that includes amygdala-striatum regions, and is responsible for automatic cognition and habitual actions. 2) Reflective system, which contains the prefrontal cortex and has been known to be involved in decision-making and impulsive control. 3) Insula cortex, which plays a key role in modulating the dynamics between these two systems. Insula interacts with top-down control networks which hijacks the ability to inhibit alcohol consumption (Noel et al., 2013). Thus insula causes a severe imbalance between the impulsive and reflective systems (Lu and Stein, 2014; Naqvi and Bechara, 2009; Noel et al., 2013). Although studies have proposed dysfunction in distinct brain regions within these systems in alcohol dependents (AD), there is little information regarding the large-scale patterns of altered functional connectivity (FC) at rest.

Resting-state fMRI enables the identification of functionally connected brain regions (Biswal et al., 1995), and data-driven approaches such as independent component analysis (ICA) allow the evaluation of functional synchronous activity between clusters (regions) for the entire RSNs. The regions within a given ICA component are strongly coherent temporally and here referred to as within-network connectivity. In spatial ICA the different components are spatially independent, but temporally dependent with each other and here referred to as between-network connectivity. In this study, the first aim was to identify differences in resting state connectivity within and among the RSNs associated with the triadic model between AD and healthy controls (HC). Besides that, we will also examine the

default model network (DMN) which has been used in examining cognitive dysfunction in neurologic and psychiatric brain disorders (Lerman et al., 2014), and is characterized by dysfunction of introspective mental processes which may be potential sources of interference during goal-directed activity. The second aim was to identify the relationship between RSN connectivity and impulsivity measures. We hypothesize that, 1) AD and HC will show a differential within-network connectivity pattern in the “impulsive”, “reflective”, salience network involving insula, and DMN that will distinguish the two groups; 2) The between-network coupling in these key systems would also be altered in AD; and 3) The changes of network FC would be correlated with key clinical measures of impulsivity.

Methods and Materials

2.1 Participants

Twenty-five alcohol-dependent (AD) subjects (8 females) with an average age of 31.9 years (range: 21 to 44, std: 7.7) and 26 healthy controls (HC) subjects (15 females) with mean age at examination of 26.3 years (range: 22 to 37, std: 3.9) were examined (Table 1). Healthy controls were recruited through newspaper advertisements and information notices distributed in the Washington, D.C. metropolitan area. Subjects comprising the alcohol-dependent group were recruited from the inpatient alcohol treatment unit at the National Institutes of Health Clinical Research Center in Bethesda, Maryland. Written informed consent to the study was obtained from all of subjects, which was approved by the Institutional Review Board of the National Institute on Alcohol Abuse and Alcoholism.

2.2 Assessments

The Structured Clinical Interview for DSM-IV-TR (SCID) was administered to all participants to determine diagnoses of alcohol dependence as well as other substance use and psychiatric disorders. The Wechsler Adult Intelligence Scale (WAIS-III) was administered to determine the intelligence quotient (IQ) of all participants. A 90 day Timeline Followback (TLFB) calendar was used to measure the frequency and amount of drinking for all subjects. The first dimension of impulsivity, trait-impulsivity, was measured by the Barratt Impulsiveness Scale (BIS-11), which is one of the most widely-used self-report measures of trait-impulsivity, refers to aspects of inattention, spontaneous actions, and lack of forethought. Another one is the UPPS-P Impulsive Behavior Scale (UPPS). This scale measures impulsivity across the Five-Factor Model of personality, measuring in this way distinct personality traits that lead to impulsive behavior. It includes Urgency (negative) (UPPS (–)), Premeditation (lack of), Perseverance (lack of), Sensation-seeking, and Positive-urgency (UPPS (+)). Second dimension of impulsivity is choice impulsivity. This deficiency was measured by delay discounting task (DDT). The DDT measures impulsivity by presenting the subject with an option between receiving a smaller immediate monetary reward or a potentially greater delayed reward (Mitchell, 1999). Participants were presented with a choice between an immediate reward and a fixed larger (\$100) but delayed (zero to 30 days) rewards. Accordingly, a discounting factor k represents the rate of discounting of the delayed outcome. As k values are not normally distributed, a natural log-transformation is usually applied and the $\ln(k)$ is used for the analyses. Higher $\ln(k)$ values mean greater

preference for immediate rewards. A smoking questionnaire helped to determine the amount and frequency of a participant's cigarette use.

2.3 Exclusionary criteria

Exclusionary criteria included pregnancy, claustrophobia, significant neurological, or medical diagnoses. Participants were instructed not to consume any alcohol for 24 hours and no more than half a cup of caffeinated beverages 12 hours prior to each scanning visit. Participants could not participate if they had a positive alcohol breathalyzer or urine drug screen on the day of the scan. HC were excluded if they met criteria for any current or past alcohol use disorder. All subjects were required to be right handed and deemed physically healthy by a clinician. Subjects were excluded if they had a positive HIV test, active suicidal or homicidal ideations, or were currently taking psychotropic medication. Since the subjects were primarily recruited for fMRI tasks a failed neuromotor examination, which evaluated motor strength, deep tendon reflexes, extraocular movements, gait, and a cerebellar assessment, was also exclusionary. This allowed the researchers to exclude subjects who may possess neurological deficiencies that could potentially compromise task driven fMRI data. AD participants could not have severe symptoms of alcohol withdrawal as determined by a Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA) score of greater than 8.

2.4 MRI Data acquisition

Whole brain Anatomical images and five minutes of closed-eyes rs-fMRI were collected at the beginning of the scan session using a 3T General Electric MRI scanner (General Electric, Milwaukee, WI) after a short 3D brain localization. High-resolution T1-weighted 3-D structural scans were acquired for each subject using an MPRAGE sequence (128 axial slices, TR = 1200ms TE = 30ms, 256×256 matrix). Resting state fMRI datasets were collected using a single-shot gradient echo planar imaging pulse sequence with thirty-four 5mm-thick axial slices acquired parallel to the anterior/posterior commissural line (TR = 2000ms, TE = 30ms, flip angle = 90° , $3.75 \text{ mm} \times 3.75 \text{ mm} \times 5.0 \text{ mm}$ voxels). Therefore, for each subject a total of 150 resting state frames (volumes) were acquired.

2.5 rs-fMRI data pre-processing

Using Functional MRI of the Brain (FMRIB)'s Software Library (www.fmrib.ox.ac.uk/fsl) we applied; 1) slice timing correction for interleaved acquisitions using Sinc interpolation with a Hanning windowing kernel; 2) motion correction; 3) non-brain removal; 4) spatial smoothing using a Gaussian kernel of full width at half maximum 5mm; 5) grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, the size of the voxels is $4 \times 4 \times 4 \text{ mm}^3$; 6) high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with $\sigma = 50\text{s}$); and 7) registration to high resolution structural MNI standard space images. We used a stringent threshold for head motion in pre-processing step. Subjects with head motion greater than 0.3 mm for translation and 0.3° for rotation between consecutive TRs were removed from the study (Power et al., 2014).

2.6 rs-fMRI connectivity analysis

We applied Probabilistic Independent Component Analysis (PICA) by using the Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC) toolbox of the FMRIB Software library (FSL) package (www.fmrib.ox.ac.uk/fsl). A temporal concatenation tool in MELODIC was used to derive group level components across all subjects. Pre-processed data were whitened and projected into a 35-dimensional subspace using PICA where the number of dimensions was estimated using the Laplace approximation to the Bayesian evidence of the model order. The whitened observations were decomposed into sets of vectors that describe signal variation across the temporal domain (time-courses) and across the spatial domain (maps) by optimizing for non-Gaussian spatial source distributions using a fixed-point iteration technique. These FC components maps were standardized into z statistic images via a normalized mixture model fit, thresholded at $z > 5$.

Two criteria were used to remove biologically irrelevant components: (1) those representing known artifacts such as motion, and high-frequency noise; and (2) those with connectivity patterns not located mainly in gray matter. Networks of interest were identified as anatomically and functionally classical RSNs upon visual inspection. The between-subject analysis was carried out using dual regression, a regression technique that back-reconstructs each group level component map at the individual subject level (Filippini et al., 2009). This technique allows for voxel-wise comparisons of resting state FC by carrying out the following steps: First, regresses the group level spatial maps into each individual's 4D dataset to obtain a set of time series. Then, regresses those individual level time series into the same 4D dataset to obtain a subject-specific set of spatial maps. Statistic inferences were then tested using FSL's randomize permutation-testing tool (Winkler et al., 2014). In cases such as fMRI data, when the null distribution is not known, permutation testing is used for inference on statistical maps (Huang et al., 2006). Voxel-wise two-sample t-test was carried out to assess statistically significant differences in FC between the groups using a 5000 non-parametric permutation testing. We utilized a threshold-free cluster enhanced (TFCE) technique to control for multiple comparisons. This method allows detecting significant clusters without having to define cluster size or the number of clusters prior to analysis. Finally, the resulting statistical maps were threshold at $p < 0.05$ FWE-corrected for multiple comparisons for the main group effect. This step generated the probabilistic maps which represent the probability of FC between AD and HC: AD maps subtracted from HC one and vice versa for all RSNs of interest. The Harvard-Oxford cortical and subcortical atlases incorporated in FSL were used to identify the anatomical regions of the resulting PICA maps.

2.7 Correlation Analysis

Within-network connectivity correlation with impulsivity measures: Using Statistical Parametric Mapping 8 (SPM8) (<http://www.fil.ion.ucl.ac.uk/spm>), for each group, individual subject maps for the independent components for the impulsive system (ASN), reflective system (OFCN, left ECN, right ECN), insula cortex (SN) and DMN (a-DMN and p-DMN), were entered as second-level regression analysis versus the impulsivity measures (BIS-11, DDT, UPPS-P) as covariate with its own IC map as mask. All within-RSN correlational

analyses were done with the cluster-level Family-wise error (FWE) corrected threshold of 0.05.

Between-network connectivity correlation with clinical measures: Even though all component maps are spatially independent, time series of the components may still have significant temporal correlations. Network interaction comparisons (Correlation coefficients, Pearson's r) between AD and HC were computed between each subject time series for the RSNs of interest that were obtained by the first stage of the dual regression procedure. These correlation coefficients were Fisher z -transformed and unpaired t -tests were conducted to compare between network connectivity in AD and HC using Statistical Analysis System (SAS software, Copyright, SAS Institute Inc. SAS and all other SAS Institute Inc.). Finally, the results were threshold at $p < 0.05$ bonferroni-corrected for multiple comparisons.

The differences in age, years of education, and IQ between AD and HC do not make for ideal comparisons. To minimize the potential confounding influence of age, years of education and IQ in these results, these parameters were used as nuisance covariates for each network of interest (Chen et al., 2007; Roberson-Nay et al., 2006; Rombouts et al., 2009; Rombouts et al., 2005). No effect of age, years of education and IQ was detected in the fMRI FC results.

Results

The ICA decomposition resulted in 35 spatial component maps, which revealed all classically identified RSNs, including DMN, visual network, somatosensory network, auditory network and artifactual components.

3.1 Addiction-related RSNs

Six networks of interests (NOI) include the “impulsive system”: the ASN, which includes the entire striatum and extends into the thalamus, hippocampus, insula, and amygdala. The “reflective” system includes three networks: (1) the right ECN, which includes the anterior cingulate cortex (ACC), medial frontal gyrus (MFG), inferior frontal gyrus (IFG), right dorsal lateral prefrontal cortex (DLPFC), right temporal cortex and portions of parietal cortex; (2) the left ECN, which includes the left DLPFC, left IFG, left dorsal ACC extending to the MFG, and portions of left temporal and parietal cortex; (3) the OFCN, which includes the OFC, MPFC, bilateral ACC, and subcallosal cortex. SN includes the insula cortex, Heschl's gyrus, and STG. In addition to the above networks, the DMN was split into posterior (pDMN) and anterior (aDMN) components in our results (Figure 1 and Table 2).

3.2 Within-network AD and HC differences

When compared with HC, AD showed significantly ($p < 0.05$, corrected) increased connectivity within “reflective” system: (1) the OFCN involving middle orbital gyrus, superior orbital gyrus, amygdala, insula, etc. (2) LECN containing angular gyrus. Also, enhanced connectivity was found in (3) ASN involving putamen, caudate, amygdala, hippocampus, subcallosal gyrus, and IFG, (4) SN involving hippocampus, insula and temporal pole. (5) aDMN including superior frontal gyrus, ACC, and superior medial gyrus,

middle frontal gyrus, and (6) pDMN in middle cingulate cortex, posterior cingulate cortex (PCC), precuneus, insula, STG, caudate, thalamus (Figure 2).

3.3 Between-network AD and HC differences

From 21 pairwise network combinations, three pairs of coupling were significantly different after correcting for multiple comparison between AD and HC and in all of them AD had increased FC compared to HC. The three pairs were: (1) LECN and ASN, (2) LECN and SN, (3) SN and ASN. Another six pairs showed trend of increased FC between AD and HC, but did not survive correction for multiple comparison. They were as follows: (1) SN and RECN, (2) RECN and ASN (3) LECN and RECN, (4) LECN and pDMN, (5) OFCN and ASN, (6) aDMN and ASN (Figure 1).

3.4 Relation between within-network FC and impulsivity

We performed correlation analyses of within-network connectivity with DDT, BIS-11, and the UPPS-P. In AD and HC, within-network FC strength was not significantly correlated with BIS-11 sum score and the DDT. UPPS (–) Urgency was significantly negatively correlated with within-network FC in ASN in AD, suggesting that when within-network FC of ASN increased, the UPPS (–) Urgency decreased. UPPS (+) Urgency was significantly negatively correlated with within-network FC in a-DMN in HC (Table 3).

3.5 Relation between network coupling and impulsivity

In AD, BIS-11 was not correlated with FC coupling. DDT was significantly positively correlated with FC coupling among LECN, SN and aDMN. UPPS (–) was significantly negatively correlated with FC coupling between OFCN and RECN, OFCN and aDMN, OFCN and pDMN ($p < 0.05$, Figure 3 and 4). In HC, between-network coupling was not significantly correlated with BIS-11, DDT, and UPPS.

Discussion

The current study sought to investigate the differences in the functional connectivity (FC) between AD and HC using ICA. Based on previous studies we hypothesized altered FC in several networks elements of which are known to have been compromised in AD. Supporting our hypothesis, AD displayed an increased pattern of both within-network FC and between-network FC coupling among RSNs involving ASN, OFCN, SN, LECN and DMN compared to HC. Also, between-network FC differences between AD and HC exhibited significant correlation with impulsivity measures such as UPPS, and DDT.

We found an increase in the intensity and extent of brain FC in AD during resting state. One explanation of this finding could be that this is a brain compensation mechanism for when a drug such as alcohol compromises the functionality of networks beyond self (within) compensation (Jansen et al., 2014). Therefore, related networks such as OFCN, ASN, etc may utilize additional cognitive resources to achieve the same level of performance. Previous studies have shown long term effects of alcohol on both gray and white matter on human brain (Durkee et al., 2013; Grodin et al., 2013; Momenan et al., 2012; Pfefferbaum et al., 2006). Also, the hyperactivation in a variety of areas including the PFC, insula,

thalamus, striatum, DLPFC, and ACC were also observed in AD patients during a multimodal stroop task (Wilcox et al., 2015). This enhanced recruitment of task-relevant areas may be interpreted as indicating an enhanced neural effort in cortical computation due to the structural damage of the brain. In our study, the increased FC may reflect the widespread structural disturbances in AD.

To date, the resting-state FC has not been extensively studied. Camchong et al. (2013a) compared the resting state connectivity using two seeds - the nucleus accumbens (NAcc) and the subgenual anterior cingulate cortex (sgACC), between abstainers and relapsers (Camchong et al., 2013a). The results showed that compared with abstainer, relapsers exhibited significantly decreased resting state synchrony within the reward network, the executive control network, and the visual network. The same group also studied functional organization in long-term abstinent alcoholics. The results revealed that compared with normal controls, long-term abstinence led to decreased synchrony within the limbic reward regions, such as the caudate and the thalamus, when using the sgACC and the NAcc seeds (Camchong et al., 2013b). Seed-based methods have also been used to identify the role of the posterior cingulate cortex in the default mode network as well as the potential for the cerebellum to be a node within the DMN. The study revealed the compromised FC in the posterior cingulate and the frontocerebellar regions in alcoholics (Chanraud et al., 2011). Those studies focused on connectivity patterns of predefined seed regions. Our work identified differences between AD and HC within large-scale brain networks and between-network coupling that are important in addiction disorders using data-driven method. More specifically, the FC in the “impulsive” system (ASN) exhibited greater FC in AD relative to HC. ASN contains the nucleus accumbens, putamen, and caudate which are known to be involved in primary reward processing. It is widely accepted that alcohol stimulates dopamine release in the ventral striatum, and thus reinforces alcohol consumption. This suggested that AD might have enhanced intrinsic neuronal activity in the ASN at rest. This finding is consistent with preclinical reports showing that alcohol induces a persistent increase in the baseline sensitivity of brain reward systems. ASN also has been reported to exhibit greater FC in smokers than normal controls. Thus, the greater ASN FC we found in AD relative to HC may represent a chronic alcohol-induced increase in baseline reward-system sensitivity. AD also exhibited greater FC in amygdala within the ASN. The amygdala is thought to primarily contribute to the acquisition, consolidation, and expression of learning of the drug-related cues that drive relapse to drug-seeking behaviors. This area is also robustly activated under drug-related cues, and was found to exhibit robust resting-state FC with affective brain areas including OFC. Our finding of enhanced FC in the amygdala may be relevant to previous studies that have demonstrated the involvement of these areas in the pathology of addiction. The next system implicated in addiction is “reflective” system which contains three networks in our study: OFCN, LECN and RECN. Our findings indicate greater within-network FC within the OFCN in AD relative to HC. The OFC and MPFC are major areas of motivation, drive, and salience evaluation, which are impaired in drug addicts and play an important role in the output of compulsive drug-seeking behaviors. Studies have shown enhanced activation in specific mesocorticolimbic dopamine system areas including OFC in alcohol-cue exposure. In the present study, significantly increased resting-state FC was found, consistent with the previous results. The ECN serves a wide range of cognitive

control functions. The prefrontal cortex is important for decision-making, inhibitory control and self-awareness, and it may become hypoactive in states of addiction. The ECN might be viewed as particularly pertinent to the field of substance dependence since it is thought to be involved in goal-directed behavior and cognitive control. The increased motivation to find and use drugs combined with an inability to inhibit drug-related behaviors is thought to represent a failure of executive control. Resting state studies have identified that this network operates in a lateralized manner. Studies have shown that Individuals with drug addictions have increased willingness to approach rewards. Approach behaviors are thought to involve executive control processes, and left prefrontal cortex is known to be more strongly involved in approach behaviors compared to right prefrontal cortex. Studies also suggest that the RECN was more strongly associated with avoidance. Compare to HC, our results showed that AD exhibited greater FC within the LECN, but there was no significant difference between AD and HC in terms of FC within the RECN. Studies have shown substance dependent individuals have greater left hemisphere connectivity in the LECN at rest. The enhanced FC within LECN we found in our results might further support the role of LECN in willingness to approach rewards.

SN plays a key function in addiction disorders that integrate incentive salience with cognitive control and decision-making processes. Specifically, the dorsal posterior insula cortex is known to represent the actual bodily changes associated with changes in motivational states and the anterior insula proposed to associate with affective and cognitive processes, and mediate subjective awareness of the craving states. In this study, we found enhanced within-network FC in bilateral anterior insula and right posterior insula in AD. This may reflect the changes of motivational states as well as the subjective awareness of the craving state in AD. We also found enhanced between-network coupling among SN, ASN and ECN. This may provide some evidence that these three networks were working together to compensate the compromised functionality caused by structural damage of alcohol. However, the FC only reflects the temporal correlations between regions, and on its face value it does not provide any direct information how these correlations are mediated. How these three systems interacted with each other was still unknown. Further studies and analyses such as mediation analysis on these three systems as well as DTI data to provide more detailed information about structural connectivity are needed to test the hypothesis proposed by Noël et al. that the insula would modulate the dynamics between the impulsive system and reflective system.

Connectivity of DMN has been linked to the core processes of human cognition, including mind-wandering and self-monitoring, the integration of cognitive and emotional processing, and introspective thoughts. As we hypothesized, compared with controls, AD showed increased FC in our study in brain regions including the PCC within the p-DMN, impairment of which is prevalent in alcohol addiction. In this study, we also found increased FC in ACC within a-DMN which has been known as an important region in cognitive control and error monitoring. This result may underline addiction-related impairment of cognitive control. Task-based fMRI studies have shown that impaired suppression of the DMN is related to poor cognitive performance such as memory formation and compromised learning of cognitive skill. Thus, a failure in this suppression would lead to a cognitive

challenge. Our results showed overall impaired DMN connectivity which may indicate the compromised suppression detected in AD.

A better understanding of the distinct neural mechanisms underlying alcohol-related impairments and their relationships with clinical and outcome measures may help in determining the pathophysiology of alcoholism and lead to the development of improved treatment strategies (Meule et al., 2011; Potenza et al., 2011). In our study, we examined the correlation of both within-network and between-network coupling and two dimensions of impulsivity. One is trait-impulsivity measured by BIS-11 and UPPS. Studies have shown that BIS-11 and UPPS cover different aspects of impulsivity (Meule et al., 2011). The other one is choice impulsivity which was measured by the DDT.

The neural mechanisms in the addicted brain are complex due to the dynamic changes of different regions and their connectivity (Volkow and Baler, 2014). Despite this complexity, a simple but key approach models neurocognitive aspects of addiction onto three neural systems and proposes this triadic model as the basis of personalized medicine (Noel et al., 2013). A similar approach focusing on impulsivity as an outcome (as measured by the DDT) has been proposed for developing improved prevention and treatment strategies (Hamilton and Potenza, 2012). These approaches center the outcomes as a result of the balance of the Impulsive and reflexive circuits. This Reflexive/Impulsive model has been used for explaining the relationship among RSN (Uddin et al., 2009). A more complex circuitry that explains the relationship among the RSNs of this reflexive-Impulse system in addiction incorporates not only the connectivity among RSNs but also the connectivity between regions within each RSN (Sutherland et al., 2012). Within this compound framework, we found that the relationship between the networks and their correlations with different measures of impulsivity is even more complex and affecting between-network FC.

The UPPS-P correlations within RSN's are for the negative-urgency score in AD subjects where it inversely correlated with the ASN mediated by the left putamen. This shows that the connectivity within the ASN network diminishes in the presence of high negative emotions, which in turn increases impulsivity. In HC, the positive-urgency score correlated negatively with the a-DMN (mediated by the precuneus) suggesting a link between down-regulation of past representations in the precuneus in order to drive the impulsive system. These results suggest that decreased connectivity in the impulsive system and the absence of a healthy down-regulation of the precuneus may weaken the ability to access and control representations of negative consequences, which is the hallmark of addiction behavior.

Figure 3 shows that in AD, the OFCN between-network connectivity with RECN, aDMN, and pDMN inversely correlate with the negative urgency measure of the UPPS (-). This implies that a weaker OFCN connectivity with the aforementioned networks might be a biomarker for higher impulsivity under intense negative emotional conditions. The DDT was significantly positively correlated with network coupling in AD, forming a closed circuit among the LECN, aDMN, and the SN. This suggests that the choice impulsivity in AD may be due to altered FC among the LECN, aDMN and the SN. This circuit has the potential for being used as a biomarker in the clinical arena (Hamilton and Potenza, 2012). BIS-11 was not significantly correlated with any network coupling in AD or HC.

Taken together, a compromised within-ASN connectivity together with an altered between-network connectivity among OFCN, ECN and DMN could be used as an intermediate phenotype in alcohol addiction. Further investigation of this possibility is needed.

Conclusion

This study provides new insight of whole brain network analysis of AD using data-driven, unbiased search for brain regions showing FC. The results demonstrated altered FC both within- and between-network FC in both “impulsive”, “reflective” systems, SN and DMN in AD, further supporting the concept that AD is a disorder affecting neural networks. We also showed that impaired connectivity in the RSNs was associated with impulsivity in AD. Our finding suggested that the altered RSN connectivity patterns might be used as a potential biomarker to detect subtle brain alterations in AD.

Limitations

In this study, most patients, as is common amongst alcohol-dependent subjects, are smokers. The FC strength might have been influenced by this confounding factor in the AD group. Therefore, further studies with either patients who are not smokers or healthy controls who are smokers should be performed to isolate the effect of alcohol from that of smoking on FC. Also, ten AD subjects have current or past use of other drugs, such as cocaine, cannabis, or opioid etc. and psychiatric disorders (Table 4). However, different subjects have different types of drug use or psychiatric disorders, and it was not consistent across the subjects. The alcohol use may still be the dominant factor contributing to the FC difference between AD and HC.

The age, year of education, and IQ differences between AD and HC is another limitation of the study. To ensure that any significant differences were not the result of these factors, we performed a group wise post-hoc analysis of covariance for each network of interest in SPM8. No voxel survival the threshold of $p < 0.05$ FWE-corrected in any of the NOIs. Therefore, we did not detect any effects of age, years of education and IQ. Since the between-group IQ has the largest difference, we repeated our analyses with 9 IQ-matched subset of the each group (AD: 110.87 ± 11.57 ; HC: 110.22 ± 12.18 ; $p = 0.9135$). Similarly we age-matched 10 subjects from each group (AD: 27.47 ± 5 ; HC: 27.47 ± 3.84 ; $p = 0.9984$). In both cases we were able to reproduce the same results as trends (as opposed to statistically significant). This result points to the fact that adding to the sample size by subjects (in both groups) that did not match in IQ (but used IQ as covariate) has not altered the results. Only that it has increased the power of the analysis.

Finally, larger sample sizes are recommended, so that more AD subjects without other drug use can be enrolled. The relatively small sample sizes mean that these findings, though informative, remain preliminary and require replication and/or larger sample study currently in progress.

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Reference

- Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. 1995; 34:537–541.
- Camchong J, Stenger A, Fein G. Resting-state synchrony during early alcohol abstinence can predict subsequent relapse. *Cerebral cortex*. 2013a; 23:2086–2099. [PubMed: 22819968]
- Camchong J, Stenger VA, Fein G. Resting-state synchrony in short-term versus long-term abstinent alcoholics. *Alcoholism, clinical and experimental research*. 2013b; 37:794–803.
- Chanraud S, Pitel AL, Pfefferbaum A, Sullivan EV. Disruption of functional connectivity of the default-mode network in alcoholism. *Cerebral cortex*. 2011; 21:2272–2281. [PubMed: 21368086]
- Chen JK, Johnston KM, Collie A, McCrory P, Ptito A. A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. *Journal of neurology, neurosurgery, and psychiatry*. 2007; 78:1231–1238.
- Durkee CA, Sarlls JE, Hommer DW, Momenan R. White matter microstructure alterations: a study of alcoholics with and without post-traumatic stress disorder. *PloS one*. 2013; 8:e80952. [PubMed: 24260518]
- Filippini N, MacIntosh BJ, Hough MG, Goodwin GM, Frisoni GB, Smith SM, Matthews PM, Beckmann CF, Mackay CE. Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106:7209–7214. [PubMed: 19357304]
- Grodin EN, Lin H, Durkee CA, Hommer DW, Momenan R. Deficits in cortical, diencephalic and midbrain gray matter in alcoholism measured by VBM: Effects of co-morbid substance abuse. *NeuroImage. Clinical*. 2013; 2:469–476. [PubMed: 24179800]
- Hamilton KR, Potenza MN. Relations among Delay Discounting, Addictions, and Money Mismanagement: Implications and Future Directions. *Am J Drug Alcohol Ab*. 2012; 38:30–42.
- Huang Y, Xu H, Calian V, Hsu JC. To permute or not to permute. *Bioinformatics*. 2006; 22:2244–2248. [PubMed: 16870938]
- Jansen JM, van Holst RJ, van den Brink W, Veltman DJ, Caan MW, Goudriaan AE. Brain function during cognitive flexibility and white matter integrity in alcohol-dependent patients, problematic drinkers and healthy controls. *Addiction biology*. 2014
- Lerman C, Gu H, Loughhead J, Ruparel K, Yang Y, Stein EA. Large-scale brain network coupling predicts acute nicotine abstinence effects on craving and cognitive function. *Jama Psychiat*. 2014; 71:523–530.
- Lu H, Stein EA. Resting state functional connectivity: its physiological basis and application in neuropharmacology. *Neuropharmacology*. 2014; 84:79–89. [PubMed: 24012656]
- Meule A, Lukito S, Vogele C, Kubler A. Enhanced behavioral inhibition in restrained eaters. *Eating behaviors*. 2011; 12:152–155. [PubMed: 21385646]
- Mitchell SH. Measures of impulsivity in cigarette smokers and non-smokers. *Psychopharmacology*. 1999; 146:455–464. [PubMed: 10550496]
- Momenan R, Steckler LE, Saad ZS, van Rafelghem S, Kerich MJ, Hommer DW. Effects of alcohol dependence on cortical thickness as determined by magnetic resonance imaging. *Psychiatry research*. 2012; 204:101–111. [PubMed: 23149031]
- Naqvi NH, Bechara A. The hidden island of addiction: the insula. *Trends in neurosciences*. 2009; 32:56–67. [PubMed: 18986715]
- Noel X, Brevers D, Bechara A. A triadic neurocognitive approach to addiction for clinical interventions. *Frontiers in psychiatry*. 2013; 4:179. [PubMed: 24409155]

- Pfefferbaum A, Adalsteinsson E, Sullivan EV. Supratentorial profile of white matter microstructural integrity in recovering alcoholic men and women. *Biological psychiatry*. 2006; 59:364–372. [PubMed: 16125148]
- Potenza MN, Sofuoglu M, Carroll KM, Rounsaville BJ. Neuroscience of behavioral and pharmacological treatments for addictions. *Neuron*. 2011; 69:695–712. [PubMed: 21338880]
- Power JD, Mitra A, Laumann TO, Snyder AZ, Schlaggar BL, Petersen SE. Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*. 2014; 84:320–341. [PubMed: 23994314]
- Roberson-Nay R, McClure EB, Monk CS, Nelson EE, Guyer AE, Fromm SJ, Charney DS, Leibenluft E, Blair J, Ernst M, Pine DS. Increased amygdala activity during successful memory encoding in adolescent major depressive disorder: An FMRI study. *Biological psychiatry*. 2006; 60:966–973. [PubMed: 16603133]
- Rombouts SA, Damoiseaux JS, Goekoop R, Barkhof F, Scheltens P, Smith SM, Beckmann CF. Model-free group analysis shows altered BOLD fMRI networks in dementia. *Human brain mapping*. 2009; 30:256–266. [PubMed: 18041738]
- Rombouts SA, Goekoop R, Stam CJ, Barkhof F, Scheltens P. Delayed rather than decreased BOLD response as a marker for early Alzheimer's disease. *NeuroImage*. 2005; 26:1078–1085. [PubMed: 15961047]
- Sutherland MT, McHugh MJ, Pariyadath V, Stein EA. Resting state functional connectivity in addiction: Lessons learned and a road ahead. *NeuroImage*. 2012; 62:2281–2295. [PubMed: 22326834]
- Uddin LQ, Kelly AMC, Biswal BB, Castellanos FX, Milham MP. Functional Connectivity of Default Mode Network Components: Correlation, Anticorrelation, and Causality. *Hum Brain Mapp*. 2009; 30:625–637. [PubMed: 18219617]
- Volkow ND, Baler RD. Addiction science: Uncovering neurobiological complexity. *Neuropharmacology*. 2014; 76(Pt B):235–249. [PubMed: 23688927]
- Whelan R, Watts R, Orr CA, Althoff RR, Artiges E, Banaschewski T, Barker GJ, Bokde ALW, Buchel C, Carvalho FM, Conrod PJ, Flor H, Fauth-Bühler M, Frouin V, Gallinat J, Gan G, Gowland P, Heinz A, Ittermann B, Lawrence C, Mann K, Martinot JL, Nees F, Ortiz N, Paillere-Martinot ML, Paus T, Pausova Z, Rietschel M, Robbins TW, Smolka MN, Strohle A, Schumann G, Garavan H, Consortium I. Neuropsychosocial profiles of current and future adolescent alcohol misusers. *Nature*. 2014; 512:185–+. [PubMed: 25043041]
- Wilcox CE, Mayer AR, Bogenschutz MP, Ling J, Dekonenko C, Cumbo H. Cognitive control network function in alcohol use disorder before and during treatment with Lorazepam. *Substance use & misuse*. 2015; 50:40–52. [PubMed: 25290463]
- Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. *NeuroImage*. 2014; 92:381–397. [PubMed: 24530839]

Figure 1.
Within-network connectivity for 6 addiction related networks and increased between-network connectivity in AD than HC

Figure 2.
Group difference of the within-network connectivity between AD and HC (red: AD>HC;
green: HC>AD), $p < 0.05$ corrected

Figure 3.
Increased (red) and decreased (blue) correlation between impulsivity (BIS-11, UPPS, and DDT) and network coupling of RSNs in AD

Figure 4.

Fisher z-transformed correlation coefficients (Z score) between Delay Discounting and network coupling (left panel top to bottom); UPPS (-) and network coupling (right panel top to bottom)

Table 1

Demographic and clinical profile of the participants in this study

	AD mean (SD)	HC mean (SD)	missing data	t	AD vs HC
N	25	26			
Gender (female)	17 (8)	11 (15)	0		
Smoker (%)	42%	0	0		
Age (years)	31.9 (7.7)	26.3 (3.9)	0	3.30	P=0.002
Education (years)	13 (2.6)	17 (2.3)	0	5.94	p < 0.001
WAIS	88.2 (15.2)	117.2 (11.1)	2	5.57	p < 0.001
Days in abstinence	16.5 (7.04)	N/A	0		
Years of dependence	6.8 (6.9)	N/A	1		
TLLFB (Drinks/week)	76.2 (57.2)	4.1 (3.6)	0	-6.3	p < 0.001
BIS-11	67.0 (14.8)	52.1 (8.2)	0	-4.4	p < 0.001
Delay Discounting	-2.7 (2.6)	-5.2 (1.8)	3	-3.3	p = 0.003

TABLE 2

Common regions of 6 addition related spatial component maps identified by ICA in both AD and HC group (MTG: Middle Temporal Gyrus; SFG: Superior Frontal Gyrus; IPL: Inferior Parietal Lobule; ITG: Inferior Temporal gyrus; SG: SupramarginalGyrus; MFG: Middle Frontal Gyrus; AG: Angular Gyrus)

Networks	Explained variance (%)	Total variance (%)	Regions	BA	Voxels	X	Y	Z	t-score max HC	t-score max AD
ASN	2.87	2.22	Putamen, Pallidum, Insula, Subcallosal Gyrus	34	842	-26	6	-4	7.64	12.57
OFC	2.8	2.17	ACC, SFG, Medial FG	10, 11	214	2	54	-8	6.67	10.26
SN	3.21	2.49	Insula, STG	13	1591	-38	-14	8	11.16	12.12
a-DMN	3.11	2.41	ACC, Medial FG	24, 32	58	-2	6	40	8.22	8.38
			SFG, Medial FG	9, 10	506	2	58	28	8.67	10.64
			PCC, Precuneus	7, 23, 30, 31	88	-6	-50	28	6.76	11.01
			MTG, STG	19, 22, 39	12	-50	-66	20	4.24	7.32
p-DMN	3.04	2.35	Precuneus, PCC	31	1167	-2	-66	24	10.88	13.89
LECN	3.12	2.42	ACC, Medial FG	9, 10, 32	12	2	42	16	5.21	5.04
			MFG, SFG	6, 8	451	-26	16	43	5.82	7.78
			AG, SG, STG, MTG, Precuneus, IPL	39, 40	344	-42	-62	32	11.54	15.39
			ITG, MTG, Fusiform Gyrus	20, 21, 37	111	-58	-42	-20	8.51	10.01
RECUN	3.23	2.5	PCC, Precuneus	23, 31	95	-2	-38	32	7.37	10.89
			AG, IPL, Precuneus, SG, MTG	39, 40	71	46	-66	36	8.49	10.2
			AG, SG, STG, MTG, IPL, Precuneus	39, 40	415	46	-62	32	10.03	13.59
			MFG, SFG	6, 8	396	26	18	48	10.15	12.6
RECUN	3.23	2.5	MFG, IFG	10, 11, 47	132	38	46	-4	7.5	9.48

Networks	Explained variance (%)	Total variance (%)	Regions	BA	Voxels	X	Y	Z	t-score max HC	t-score max AD
			PCC, precuneus	23, 31	54	6	-34	32	7.01	9.65
			MTG, ITG	20, 21	31	62	-34	-12	5.42	8.15

Networks that showed significant correlation between within-network FC and impulsivity, the a-DMN negatively correlated with UPPS(+) Urgency in precuneus in HC, and the ASN negatively correlated with UPPS(-) Urgency in putamen in AD

TABLE 3

Impulsivity	Networks	Group	FWE-corr p	Cluster size	T	Z	mm	mm	mm	Regions
UPPS (+)	a-DMN	HC (-)	0.006	26	5.4	4.3	-18	-58	28	Precuneus
UPPS (-)	ASN	AD (-)	0.047	13	4.2	3.6	-22	2	12	Putamen
					3.8	3.3	-26	-10	8	Putamen

TABLE 4

Comorbidity of other drug use and psychiatric disorders (detail)

	Dependence		Abuse	
	current	past	current	past
Cannabis	2	8	1	3
Cocaine	0	2	0	8
Opioid	0	0	0	2
Hallucinogen	0	2	0	2
Amphetamine	0	0	0	1
Sedative, hypnotic, or anxiolytic	0	0	0	1

Psychiatric Disorders					
	AD		HC		
	Current	Past	Current	Past	
Generalized Anxiety Disorder	3	1	0	0	
Social Phobia	1	0	1	1	
Alcohol-Induced Mood Disorder	5	2	0	0	
Ancohol-Induced Anxiety Disorder	3	2	0	0	
Substance-Induced Anxiety Disorder	1	0	0	0	
Anorexia Nervosa	0	2	0	0	
Major Depressive Disorder	3	3	0	1	
Posttraumatic Stress disorder	9	1	0	1	
Agoraphobia Without History of Panic Disorder	1	0	0	0	
Specific Phobia	1	0	0	0	
Dysthymic Disorder	0	1	0	0	
Mood Disorder Due to General Medical Condition	0	0	0	1	