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Resting State Synchrony in Short-Term versus Long-Term Abstinent Alcoholics

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Abstract

BACKGROUND—We previously reported that when compared to controls, long-term abstinent alcoholics (LTAA) have increased resting state synchrony (RSS) of the inhibitory control network and reduced synchrony of the appetitive drive network, and hypothesized that these levels of synchrony are adaptive, and support the behavioral changes required to maintain abstinence. In the current study, we investigate whether these RSS patterns can be identified in short-term abstinent alcoholics.

METHODS—Resting state functional magnetic resonance imaging data were collected from 27 short-term abstinent alcoholics (STAA), 23 LTAA and 23 non-substance abusing controls (NSAC). We examined baseline RSS using seed-based measures.

RESULTS—We found ordered RSS effects from NSAC to STAA and then to LTAA within both the appetitive drive and executive control networks: increasing RSS of the executive control network, and decreasing RSS of the reward processing network. Finally, we found significant correlations between strength of RSS in these networks and (a) cognitive flexibility and (b) current antisocial behavior.

DISCUSSION—Findings are consistent with an adaptive progression of RSS from short- to long-term abstinence so that, compared to normal controls, the synchrony (a) within the reward network progressively decreases and (b) within the executive control network progressively increases.

Keywords

abstinence; alcohol; fMRI; functional connectivity; resting state networks

Introduction

Alcohol dependence is thought of as a disorder with an overwhelming impulsive and compulsive “drive” towards alcohol consumption (Kamarajan et al. 2005), and an inability to “hit the brakes”, or inhibit alcohol consumption despite negative biological, psychological, legal, and social consequences (American Psychiatric Association 1994). Functional neuroimaging studies suggest that these aspects of alcohol dependence

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correspond to differences (from non-alcoholic controls) in brain function and organization within both top-down and bottom-up networks that mediate inhibitory control of behavior and appetitive drive toward consummatory behavior (Akine et al. 2007; Gilman et al. 2008; Li et al. 2009; Vollstadt-Klein et al. 2010). These brain function and organization differences from controls vary depending on whether an alcoholic is actively drinking, is in early abstinence or in long-term abstinence.

Neural networks in active alcohol dependence

FMRI studies have reported that when actively drinking alcoholics view alcohol cues, crave alcohol, or consume alcohol, they show increased activity in the bottom-up appetitive drive network, particularly in the nucleus accumbens (Ihssen et al. 2011; Myrick et al. 2004; Schacht et al. 2011). The nucleus accumbens (NAcc), an important limbic region that mediates appetitive drive and behavior towards rewards, is presumably involved in the lack of behavioral flexibility necessary to generate new adaptive behavior and the inability to extinguish alcohol-related habits (Chen et al. 2011). Studies have suggested that involvement of brain regions within the bottom-up network differ as a function of the development of dependence. It has been proposed that as alcohol use shifts from habit to compulsion, there is a shift in the involvement of limbic regions, particularly from nucleus accumbens to caudate and putamen (Everitt and Robbins 2005; Vollstadt-Klein et al. 2010).

Functional differences from non-alcoholic controls within the top-down executive control network have been identified in actively drinking alcoholics, particularly those differences associated with poor regulation of behavior and emotion, a core aspect of alcohol dependence (Berking et al. 2011; Fox et al. 2008). Dysfunctional emotion regulation in alcoholics (e.g., extremes in emotional responsiveness to social situations, negative affect, and mood swings) has been associated with prefrontal dysfunction (Lyvers 2000), particularly in the subgenual anterior cingulate cortex (sgACC) (Salloum et al. 2007).

Neural networks in abstinence

While brain functional differences from controls have been examined in actively using alcoholics, there is also evidence suggesting that there are identifiable differences from normal controls in *abstinent* alcoholics, which may be related to the length of abstinence. The characteristics of top-down and bottom-up networks at different stages of abstinence (short- or long-term abstinence) from alcohol may help identify brain mechanisms that support the cessation of drinking and the development of long-term abstinence.

Short-term abstinence

Studies that have examined reward processing during early abstinence from alcohol have identified differences from controls in brain function and organization. An fMRI study using the monetary incentive delay task (MIDT) in 5–37 day abstinent alcoholics found reduced NAcc activation when processing monetary reward and increased NAcc activation when viewing alcohol related cues in alcoholics compared to controls (Wrase et al. 2007). Results from that study suggest that salience of alcohol cues is present during early stages of abstinence. Another fMRI study in 7–14 day abstinent alcoholics found that reduced NAcc activation during anticipation of reward was associated with higher impulsivity and alcohol craving, suggesting that differences in NAcc activity may impact the maintenance of abstinence (Beck et al. 2009).

Long-term abstinence

There is evidence from the task-evoked fMRI literature supporting the existence of compensatory mechanisms in top-down and bottom-up networks in long-term abstinence. A

recent study by Nestor et al. (2011) compared task-evoked brain activity between long-term abstinent smokers, current smokers and non-smoking controls during a task that required a stimulus-response selection based on the colored border of a picture, with the picture (distractor) being either a smoking cue, a neutral or an evocative picture. Even though they did not report a condition (picture type) by group interaction in task-evoked brain activity, they did find a main effect of group. Long-term abstinent smokers showed increased task-evoked activity in executive control regions (e.g. dorsolateral prefrontal cortex, anterior cingulate cortex) and lower activity in reward processing regions (e.g. nucleus accumbens) when compared to current smokers and non-smoking controls. Since long-term abstinent smokers had slower responses, but with accuracy comparable to non-smoking controls (active smokers performed less well), Nestor et al (2011) suggested that long-term abstinent smokers recruit frontal regions to increase regulation of their responses to achieve performance (Nestor et al. 2011). Their results suggest compensatory mechanisms in long-term abstinence (from addictive substances such as nicotine or alcohol), in which individuals ostensibly avoid relapse by enhancing the involvement of executive control regions and attenuating the involvement of reward processing regions when responding to the environment.

A study by Dresler et al (2011) provided evidence suggesting that the engagement of executive control regions during task performance was a function of abstinence length. They found no significant differences in frontal task-evoked brain activity during a verbal fluency task between long-term abstinent alcoholics (abstinent for 264.75 ± 198.24 days) and controls. Since *short-term* abstinent alcoholics in the same study had significantly lower frontal brain activity when compared to controls (and to long-term abstinent alcoholics), the authors proposed that there is an increase in task-related frontal brain activity with continued abstinence such that long-term abstinent alcoholics are comparable to healthy controls.

Resting state synchrony in alcohol dependence

While the above studies provide evidence of task-related brain functional differences in alcohol dependent samples vs. controls, the examination of resting state networks provides a different perspective on functional brain organization in alcohol dependence. The examination of the brain synchrony patterns during rest allows us to investigate the organization of neural networks that likely impact the network's response to the environment (Biswal et al. 1997; Mennes et al. 2011).

The two studies that have compared resting state synchrony (RSS) between abstinent alcoholics and controls (J. Camchong et al. 2012; Chanraud et al. 2011) have identified evidence for compensatory mechanisms in abstinent alcoholic resting state networks. Chanraud et al (2011), who focused on examining the default mode network (with a seed in posterior cingulate gyrus (PCG)), found evidence for a compensatory mechanism in the level of synchrony between PCG and cerebellum in 5–126 day abstinent alcoholics. While synchrony between PCG and cerebellum was lower in abstinent alcoholics than in controls during rest, synchrony between these regions was higher in abstinent alcoholics than controls when performing a spatial working memory task (a potential compensatory mechanism needed to achieve similar working memory performance levels as controls). Even though Chanraud et al (2011) examined RSS in abstinent alcoholics, they did not examine synchrony within resting state networks that are directly relevant to alcohol dependence, such as the top-down (inhibitory control) or the bottom-up (reward) networks. A previous study from our group focused on examining resting state networks in the inhibitory control (seeded in subgenual anterior cingulate) and the reward (seeded in NAcc) networks in long-term abstinent alcoholics (days abstinent: $M=2888.78$, $SD=2848.14$) (J. Camchong et al. 2012). We found increased synchrony in the inhibitory control network and reduced synchrony in the appetitive drive reward network in long-term abstinent alcoholics

when compared to controls. Our previous resting state findings suggest that there are adaptive mechanisms in functional organization at rest in long-term abstinence that may facilitate the behavioral control required to maintain abstinence (i.e., enhanced inhibitory control and reduced drive).

Purpose of present study

The goal of the present study was to investigate whether the differences from controls in long-term abstinent alcoholics in the strength of synchrony of inhibitory control and appetitive drive networks are present in short-term abstinent alcoholics. We hypothesized that short-term abstinent alcoholics (STAA) will be intermediate between non-substance abusing controls (NSAC) and long-term abstinent alcoholics (LTAA) in synchrony of the executive control and appetitive drive networks. Further, given the relationship between RSS and behavior (Mennes et al. 2010; Mennes et al. 2011; Zhu et al. 2011), we hypothesized: (1) that differences in RSS involving executive control regions in the STAA group will be positively correlated with performance on a task that assesses cognitive flexibility, an aspect of executive control and that (2) differences in RSS involving reward processing regions in the STAA group will be positively correlated with behavior ruled by appetitive drive, such as antisocial behavior.

Materials and Methods

Participants

Twenty-seven STAA (abstinent 72.59 ± 18.36 days) were compared to gender and age comparable LTAA ($n=23$, abstinent 2888.78 ± 2848.14 days) and NSAC ($n=23$). LTAA and NSAC samples were from our prior publication (J. Camchong et al. 2012)). All subjects were contemporaneously recruited from the island of Oahu (Table 1). STAA and LTAA were recruited through advertisements and fliers posted in various treatment programs including Alcoholic Anonymous meetings. STAA and LTAA met DSM-IV lifetime criteria for alcohol dependence (American Psychiatric Association 1994), but not for lifetime abuse or dependence on any other drugs of abuse (other than nicotine or caffeine). All subjects' substance use history was gathered using the Lifetime Drinking History instrument designed by Skinner and Sheu (1982), administered separately for alcohol (Table 2) and for each other substance used (including nicotine, Table 1). In addition, subjects completed the computerized Diagnostic Interview Schedule (C-DIS) (Levitan et al. 1991) to ascertain externalizing, anxiety or mood disorder diagnoses and symptom counts (Table 3). Participants also completed the MMPI Psychopathic Deviance subscale and the California Psychological Inventory to measure antisocial disposition (Table 4).

A breathalyzer test to screen for alcohol (Alco-Sensor IV, Intoximeters, Inc., Saint Louis, MO) and a saliva screen for drugs (Oral Fluid Drug Screen Device, Innovacon, Inc., San Diego, CA) was performed for all subjects on each testing day, with negative findings required for participation (no subjects failed the screens). Participants received monetary compensation for their participation. Exclusion criteria for all groups included: a) lifetime or current dependence on any other drug of abuse; b) significant history of head trauma or cranial surgery; c) current or lifetime history of diabetes, stroke, or hypertension that required medical intervention; d) current or lifetime history of a significant neurological disorder; e) clinical or laboratory evidence of active hepatic disease; f) clinical evidence for Wernicke-Korsakoff syndrome, and g) lifetime diagnosis of schizophrenia or schizophreniform disorder (as assessed by the C-DIS).

Imaging data acquisition

As previously reported (J. Camchong et al. 2012; J Camchong et al. 2012), resting functional magnetic resonance (fMRI) data were collected using a twelve-channel head coil on a Siemens Tim Trio 3.0 T scanner (Siemens Medical Solutions, Erlangen, Germany) located at Queen's Medical Center in Honolulu. Subjects were instructed to lay motionless in the scanner with their eyes closed. The imaging sequence was a gradient-echo spiral in/out sequence with parameters of TE=30 ms, TR=2000 ms, flip angle=60°, 28 interleaved axial 5 mm thick contiguous slices, FOV=22 cm, and a 3.44×3.44 mm in-plane resolution (64×64 matrix size) (Glover and Law 2001; Noll et al. 1995). Images were reconstructed using a custom gridding reconstruction program with a field map based off resonance correction (Jackson et al. 1991; Noll et al. 1991). Spiral-in images and spiral-out images were magnitude squared summed to improve signal-to-noise and to recover signal loss caused by susceptibility variations in the brain. FMRI session included a total 123 volumes for a total scan time of 4:06. The first three volumes were discarded from data analysis to ensure magnetization reached steady state. The last volume was acquired with a 31 ms TE for the field map measurement and was also excluded from fMRI analysis.

A high-resolution T1-weighted structural image was also acquired using an MPRAGE sequence with parameters of TE=4.11 ms TR=2200 ms, flip angle=12°, 160 sagittal slices, slice thickness=1 mm, slice gap=0.5 mm, FOV=256 mm. The T1-weighted image was used in the data analysis for image registration purposes.

FMRI data preprocessing

As previously reported (J. Camchong et al. 2012; J Camchong et al. 2012), all imaging data was preprocessed using the AFNI (Analysis of Functional NeuroImages (Ward 2000)) and FMRIB Software Libraries (FSL; FMRIB, Oxford, United Kingdom). Preprocessing consisted of: slice time correction; three-dimensional motion correction; temporal despiking; spatial smoothing (full-width at half maximum=6mm); mean-based intensity normalization; temporal band-pass filtering (0.009–0.1 Hz); and linear and quadratic detrending. Probabilistic independent component analysis (PICA) was conducted for each individual to denoise individual data by removing components that represented noise such as head motion ("rim-like" artifacts around the brain), scanner artifacts (e.g. slice dropouts, high-frequency noise, and field inhomogeneities), and physiological noise (e.g. respiration, cardiac frequencies, white matter or cerebrospinal fluid fluctuations) as previously reported (Camchong et al. 2011; J. Camchong et al. 2012; J Camchong et al. 2012). Noise components were selected by spatial and temporal characteristics detailed in the MELODIC (FSL) manual (<http://fmrib.ox.ac.uk/fslcourse/lectures/melodic.pdf>) and based on (Kelly et al. 2010) for selection criteria of noise components. An ANOVA conducted to look for differences in the sum of total percent variance accounted for in components removed showed no significant effect of group ($F(1,70)=2.83$, $p=0.07$).

All image registrations were conducted with FSL-FLIRT (FMRIB's Linear Image Registration Tool) which uses an automated linear (affine) registration (Jenkinson et al. 2002). First, each individual's preprocessed and denoised fcMRI data was registered to individual's high-resolution T1-weighted structural image (with 6 degrees of freedom) which generated a transformation matrix file. High-resolution T1-weighted structural image was then registered to a standard Montreal Neurological Institute (MNI-152) brain (with 12 degrees of freedom) which generated a second transformation matrix file. These two transformation matrices were used to register each individual's preprocessed and denoised fcMRI data to MNI standard space to be used for group analysis.

Resting state individual-level analysis

As previously reported (J. Camchong et al. 2012; J Camchong et al. 2012), nucleus accumbens (NAcc) and subgenual anterior cingulate cortex (sgACC) were selected as seeds to examine RSS within bottom-up and top-down networks (Figure 1). For each participant and for each seed (sgACC and NAcc), a multiple regression analysis (FSL-FEAT (Smith et al. 2004)) on the denoised data was performed. This analysis generated a map of statistical parameter estimates (PEs) for each voxel, for each individual, for each seed. All voxels in the PEs maps showed the degree of positive or negative correlations with the corresponding seed time-series for each seed for each participant. Correlation values at each voxel were transformed to z-scores.

Resting state group-level analysis

Because the purpose of the present study was to investigate whether compensatory mechanisms previously found in LTAA (J. Camchong et al. 2012) are present in STAA, we focused our group-level analysis within specific clusters in which we previously found RSS differences between LTAA and NSAC (Table 5). We conducted an analysis of variance (ANOVA) on mean z-scores (representing strength of RSS with the seed) within the clusters in Table 5 as dependent variables and group membership as the fixed factor. The grouping factor was coded as NSAC=0, STAA = 1, and LTAA = 2. (Linear contrast tested for ordering of the dependent measures: NSAC < STAA < LTAA, with equal magnitude of differences between NSAC and STAA vs. STAA and LTAA). Given three groups with 2 degrees of freedom, the quadratic contrast tested for differences between the groups that were independent of the linear contrasts. *Post hoc* Tukey tests were conducted to identify significant differences in paired comparisons between STAA and LTAA and between STAA and NSAC.

Behavioral task

As described in our previous manuscript (J. Camchong et al. 2012) all subjects performed the intradimensional/extradimensional set shift task (IED, (Cambridge Cognition 2006), a task that assesses cognitive flexibility, an important behavioral construct in abstinent alcoholics' ability to change and adapt social behavior. In a separate session before the scan, participants completed the IED task which assessed an individual's ability to change a learned behavior when response contingencies changed.

Correlates of RSS

In order to minimize the number of correlations examined, the average RSS for regions within the executive control network ((MacDonald et al. 2000; Kerns et al. 2004); sgACC and DLPFC) and for regions within the limbic reward processing network ((Everitt and Robbins 2005); caudate, thalamus, nucleus accumbens) were calculated. Two non-parametric (Spearman's Rho) correlations were examined. First, based on results from our previous resting fMRI manuscript (Camchong *et al.* 2012) where we found a significant positive correlation between RSS in the executive control network and IED performance (cognitive flexibility) in the LTAA group, we investigated this same relationship in STAA (directional hypothesis: 1-tailed). Second, our group recently reported that while antisocial *disposition* (antisocial thinking or proneness) was elevated in both short-term and long-term abstinent alcoholics when compared to non-substance abusing controls, only short-term abstinent alcoholics showed elevated antisocial *behavior* (current symptom count of antisocial personality disorder - ASPD), whereas long-term abstinent alcoholics did not differ from non-substance abusing controls (Fein and Fein 2012). Based on this observation, we investigated whether STAA have a positive relationship between average RSS strength

within the reward network and the current antisocial behavior (ASPD symptom count; directional hypothesis: 1-tailed), but not with measures of antisocial disposition.

Results

The group (STAA, LTAA, NSAC) X RSS ANOVA showed significant linear trend effects of group for all clusters examined (Table 6).

Significant linear trend of higher RSS of executive control regions—There were significant linear increases in RSS between DLPFC and both the NAcc and sgACC seeds when contrasting NSAC, STAA, and LTAA (Table 6, Figures 2 and 3).

Significant linear trend of lower RSS of reward processing regions—There were significant linear decreases in RSS between both the NAcc and sgACC seeds and regions in which we had previously found to be significantly lower RSS in LTAA than NSAC (J. Camchong et al. 2012). This pattern was present examining appetitive drive network synchrony between: (a) NAcc and inferior parietal lobule (Figure 4B), (b) NAcc and bilateral caudate (Figure 4B), (c) NAcc and bilateral anterior nucleus of the thalamus (Figure 4B), and (d) sgACC and anterior nucleus of the thalamus (Figure 5).

Significant linear and non-linear effects in RSS—There was a significant linear and nonlinear trend in RSS between the NAcc seed and medial dorsal thalamus (Figure 4B). While LTAA had significantly lower RSS between these regions than NSAC (as previously reported (J. Camchong et al. 2012)), STAA did not. STAA had significantly higher RSS between these regions when compared to LTAA.

Behavioral task performance

Intradimensional/extradimensional set shift task (IED) task performance: ANOVA results showed no significant differences in task performance: in number of blocks completed successfully, number of trials needed to complete a block, or adjusted total number of errors across groups (Table 7).

RSS behavioral correlates in STAA group

The STAA group showed a strong trend toward a positive correlation between IED performance and average strength of RSS within the executive control network (Spearman's $Rho=0.368$, $p=0.059$) (Figure 6). STAA with higher RSS within the executive control network (higher z-scores) had better IED performance. STAA also had a significant positive correlation between the number of current ASPD symptoms and average RSS strength within the reward network (Spearman's $Rho=0.411$, $p=0.033$). As hypothesized, there were no significant correlations between average RSS in the reward network and MMPI's Psychopathic Deviance subscale (Spearman's $Rho=0.100$, $p=0.62$) or Socialization scores of the California Psychological Inventory (Spearman's $Rho=-0.064$, $p=0.75$).

Discussion

The main goal of the present study was to investigate whether functional organization differences within top-down and bottom-up neural networks previously identified in long-term abstinent alcoholics (LTAA) (J. Camchong et al. 2012) could be identified in short-term abstinent alcoholics (STAA). We found significant abstinence duration ordered RSS effects in both networks: increasing RSS (NSAC < STAA < LTAA) of top-down executive control regions (i.e. DLPFC), and decreasing RSS (NSAC > STAA > LTAA) of bottom-up

reward processing regions. We also found that (1) RSS strength of regions within the executive control network was correlated with cognitive flexibility and that (2) RSS within the reward network was correlated with the number of current antisocial symptoms.

Ordered effects of higher RSS in executive control network during abstinence in alcoholics

We had previously reported that LTAA have significantly higher RSS between DLPFC and both resting state network seeds (NAcc and sgACC) when compared to NSAC (J. Camchong et al. 2012). We now reported that STAA also show higher RSS between DLPFC and both seeds when compared to NSAC, but to a lesser degree than LTAA (Figures 2 and 3). Based on current and previous results (J. Camchong et al. 2012), we propose that abstinent alcoholics have a need to increase synchrony of executive control regions (i.e. DLPFC) throughout the course of abstinence in order to better manage executive control needs for successful long-term abstinence.

Behavioral correlates of average RSS strength within the executive control network provide supporting evidence to the above claim. Even though groups did not differ in performance levels in the IED task, we found that higher average strength of RSS within regions of the executive control network was associated with better cognitive flexibility in the STAA group. A recent study by Chanraud et al (2012) in which they examined both strength of RSS and task-related brain signal during working memory in abstinent alcoholics (at least 30 days abstinent), reported that abstinent alcoholics have increased DLPFC engagement both during rest as well as when performing a working memory task when compared to healthy controls. Based on the above findings as well as previous reports on the relationship between strength of RSS and measured behavior (Koyama et al. 2011), we propose that present associations found between RSS strength of executive control regions and behavior may reflect an ongoing compensatory mechanism in which individuals with higher RSS synchrony of executive control regions (i.e. better brain functional organization (Mennes et al. 2011)) are better prepared to exert executive control when needed.

Ordered effects of lower RSS during abstinence in alcoholics

We found abstinence duration ordered effects of decreasing RSS between reward processing regions when contrasting NSAC, STAA and LTAA (Figures 4 and 5). We had previously reported that LTAA have significantly lower RSS in regions shown in Figures 4 and 5 when compared to NSAC (J. Camchong et al. 2012). We now reported that STAA also show lower RSS in these reward processing regions when compared to NSAC, but to a lesser degree than LTAA. Based on current and previous results (J. Camchong et al. 2012), we propose that abstinent alcoholics disengage interactions of regions known to be part of the bottom-up reward network in order to avoid the probability of falling back into relapse. Importantly, this disengagement may be a function of abstinence length.

We propose that the engagement of reward processing regions varies depending on the stage of alcohol dependence. First, studies have reported an increased engagement of reward processing regions during the establishment of alcohol dependence. For example, NAcc is recruited to mediate the establishment and definition of the rewarding effects of alcohol, thalamus is recruited to relay this information to cortex to orient attention (e.g. parietal cortex) and goal-directed behavior towards the reward, and, if this behavior is repeated numerous times, caudate is recruited to form and maintain habits (Everitt and Robbins 2005; Vollstadt-Klein et al. 2010). Hence, active alcoholics show increased engagement of reward processing regions (Ihssen et al. 2011; Myrick et al. 2004; Schacht et al. 2011). Our results on short- and long-term abstinent alcoholics provide evidence that the engagement of reward processing regions is attenuated during the course of abstinence (when reward processing

behaviors are inhibited), and that this attenuation progresses with length of abstinence. These RSS differences may indicate a regulatory mechanism found in abstinent alcoholics that arises during the course of abstinence to minimize organized interaction of regions that process reward to minimize appetitive drive and avoid relapse.

We have previously shown that antisocial behavior is reduced in long-term abstinence (Fein and Fein 2012). While most studies in the literature have reported an association between antisocial behavior and attenuated task-evoked brain activity in executive control regions or attenuated synchrony of executive control regions (Juárez et al. 2012; Motzkin et al. 2011; Muller et al. 2003; Pujol et al. 2011; Yang et al. 2008), there are a few studies that have reported that antisocial behavior is also associated with heightened reactivity of reward processing regions (Bjork et al. 2012; Buckholtz et al. 2010). Our current finding of a positive association between RSS within the reward network and current antisocial symptoms in STAA is novel, suggesting a link between current antisocial behavior and increased RSS within brain regions known to process reward. It is important to note that while antisocial *behavior* was correlated with average reward network RSS, measures of antisocial *disposition* (i.e. MMPI's Psychopathic Deviance subscale and Socialization scores of the California Psychological Inventory), which do not differ between short- and long-term abstinence (Fein and Fein 2012), were not correlated, presumably because these measures reflect a stable trait that does not change with abstinence.

A limitation of the current study is its cross-sectional design, which does not assess changes over time in individuals. It is possible that the results are at least partially due to selective survivorship (i.e., individuals with lower appetitive drive RSS and higher executive control RSS are more likely to stay abstinent). Only longitudinal studies can definitively establish changes with individuals with duration of abstinence. Another issue to consider is that while there is strong evidence that synchrony of neural networks during rest is related to behavior measured outside of the scanner (Mennes et al. 2010; Mennes et al. 2011; Zhu et al. 2011), future research needs to examine how these RSS findings relate to brain activation in response to the environment.

In conclusion, we believe that current results provide evidence for short-term abstinent alcoholics having a different pattern strength of appetitive drive and inhibitory control networks when compared to non-alcoholic controls - with this pattern being intermediate between controls and long-term abstinent alcoholics. Findings are consistent with an adaptive linear progression of resting state synchrony strength in these networks with duration of abstinence so that (a) synchrony of executive control regions progressively increases and (b) synchrony of reward processing regions progressively decreases. In addition, (a) enhanced synchrony between executive control regions was associated with better cognitive flexibility and (b) lack of disengagement of synchrony between reward processing regions was associated with more current antisocial symptoms in short-term abstinence. Current results provide important evidence on the key role of the top-down and bottom-up networks that mediate abstinence during alcohol dependence.

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Figure 1. (A) Nucleus accumbens and (B) subgenual anterior cingulate cortex (ACC) seeds used to examine strength of resting state synchrony overlaid on Montreal Neurological Institute brain in neurological orientation (right is right).

Figure 2.

(A) Three-dimensional MNI brain in neurological orientation with slice cut at $z=22$ showing region (in blue) in which LTAA showed significantly higher strength of RSS than NSAC in the NAcc network in our previous study (J. Camchong et al. 2012). (B) Bar graph showing a significant linear trend between groups in strength of RSS between NAcc and left DLPFC: intermediate in STAA (green bar) when compared to LTAA (beige bar) and NSAC (blue bar). Red lines represent significant post-hoc differences between groups. MNI, Montreal neurological institute; LTAA, long-term abstinent alcoholics; STAA, short-term abstinent alcoholics; NSAC, non-substance abusing controls; RSS, resting state synchrony; NAcc, nucleus accumbens; DLPFC, dorsolateral prefrontal cortex.

Figure 3.

(A) Three-dimensional MNI brain in neurological orientation with slices cut at $z=21$ and $z=43$ showing regions (in blue) in which LTAA showed significantly higher strength of RSS between sgACC and DLPFC than NSAC in our previous study (J. Camchong et al. 2012).

(B) Bar graph showing a significant linear trend between groups in strength of RSS between sgACC and right DLPFC: intermediate in STAA (green bar) when compared to LTAA (beige bar) and NSAC (blue bar). Red lines represent significant post-hoc differences between groups. MNI, Montreal neurological institute; LTAA, long-term abstinent alcoholics; STAA, short-term abstinent alcoholics; NSAC, non-substance abusing controls; RSS, resting state synchrony; sgACC, subgenual anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex.

Figure 4.

(A) Three-dimensional MNI brain in neurological orientation with slices cut at $z=57$, $z=14$, $z=10$ showing regions (in orange) in which LTAA showed significantly lower strength of RSS with NAcc than NSAC in our previous study (J. Camchong et al. 2012). (B) Bar graphs show RSS with NAcc in STAA (green bars), LTAA (beige bars) and NSAC (blue bars). Red lines represent significant post-hoc differences between groups. MNI, Montreal neurological institute; LTAA, long-term abstinent alcoholics; NSAC, non-substance abusing controls; RSS, resting state synchrony; NAcc, nucleus accumbens; MD-thal, medial dorsal thalamus; AN-thal, anterior nucleus of the thalamus; IPL, inferior parietal lobule.

Figure 5.

(A) Three-dimensional MNI brain in neurological orientation with slice cut at $z=12$ showing region (in orange) in which LTAA showed significantly lower strength of RSS between sgACC and bilateral anterior nucleus of the thalamus than NSAC in our previous study (J. Camchong et al. 2012). (B) Bar graph shows a significant linear trend between groups in strength of RSS between NAcc and AN-thal: intermediate in STAA (green bars) when compared to LTAA (beige bars) and NSAC (blue bars). Red lines represent significant post-hoc differences between groups. MNI, Montreal neurological institute; LTAA, long-term abstinent alcoholics; NSAC, non-substance abusing controls; RSS, resting state synchrony; ACC, anterior cingulate cortex; AN-thal, anterior nucleus of the thalamus.

Executive control RSS correlated with cognitive flexibility in STAA

Figure 6.

Regression plot showing a significant positive correlation between strength of RSS in executive control regions and IED (intradimensional/extradimensional set-shift task) performance. Higher IED performance score reflects better performance (lower error rate). Individual STAA participants are represented by circles. RSS, resting state synchrony; STAA, short-term abstinent alcoholics.

Table 1

Demographics, symptom counts, and other substance use in STAA, LTAA, and NSAC.

Characteristic	STAA (n = 27)			LTAA (n = 23)			NSAC (n = 23)			Sig.	STAA vs LTAA Odds Ratio
	Mean	or	n	Mean	or	n	Mean	or	n		
Age, (yrs)	49.27			48.46			47.99			0.26	0.77
Education, (yrs)											
Subject	14.56			13.22			14.74			3.45	0.04 ^a
Female, n (%)	9	33.33%		8	34.78%		8	34.78%		--	0.96
Nicotine Use											
History, n (%)	9	33.33%		11	47.83%		3	13.04%		--	0.70
Current, n (%)	7	25.93%		7	30.43%		2	8.70%		--	0.85
Additional Substances Used											
Cocaine, n (%)	0	--		0	--		1 ^b	4.35%		--	--
Methamphetamine, n (%)	0	--		0	--		0	--		--	--
Marihuana, n (%)	3 ^b	11.11%		4 ^b	17.39%		1 ^b	4.35%		--	0.64

* p<0.05

^a Tukey Post-Hoc test showed that only LTAA had significantly lower number of years of education than NSAC (p=0.028). STAA level of education was not significantly different from NSAC (p=0.375) or LTAA (p=0.354).

^b recreational substance use only, no Ss met criteria for abuse or dependence; subjects had been abstinent from these substances for an average of 18 years at the time of assessments.

STAA, short-term abstinent alcoholics; LTAA, long-term abstinent alcoholics; NSAC, non-substance abusing controls; SD, standard deviation.

Table 2

Alcohol use measures of STAA and LTAA.

Characteristic	STAA (n = 27)		LTAA (n = 23)		t	Sig (2-tailed)	Effect Size Partial Eta ²
	Mean	SD or n	Mean	SD or n			
Age started drinking, (yrs)	18.07	5.42	15.17	4.12	4.14	0.047*	0.81
Age when consumption reached heavy use (yrs)	26.73	1.83	23.08	1.91	1.91	0.17	0.04
Proportion of 1 st degree relatives who are problem drinkers (total number/number of relatives)	0.31	0.30	0.33	0.27	0.05	0.82	0.001
Average Dose (Lifetime; standard number of drinks per month)	193.88	250.57	188.51	163.03	0.11	0.92	0.0002
Dose During Peak Use (number of drinks per month)	378.84	451.05	328.65	258.78	0.24	0.62	0.005
Length of Abstinence (number of days)	72.59	18.36	2888.78	2848.14	25.51	0.00001^a	0.352

* p<0.05

^a statistical comparisons are inappropriate since the variable is related to selection criteria

STAA, short-term abstinent alcoholics; LTAA, long-term abstinent alcoholics; SD, standard deviation.

Table 3

Current and lifetime psychiatric diagnoses in STAA and LTAA. Data for non-substance abusing controls can be found in our previous paper (J. Camchong et al. 2012)

Psychiatric Diagnoses	Current Diagnoses Count				Lifetime Diagnoses Count			
	NSAC (n=23) Count (n)	LTAA (n=23) Count (n)	STAA (n=27) Count (n)	LTAA vs STAA Odds Ratio	NSAC (n=23) Count (n)	LTAA (n=23) Count (n)	STAA (n=27) Count (n)	LTAA vs STAA Odds Ratio
Internalizing disorders	2	3	12	0.30 [*]	6	16	18	1.04
Mood	2	3	11	0.32 [*]	6	13	16	0.95
Dysthymia	0	0	0	N/A	0	1	0	∞
Manic Episode	0	0	3	∞	0	2	4	0.59
Hypomanic	0	0	0	N/A	0	0	0	N/A
Major Depressive Disorder	1	2	8	0.29	5	10	12	0.98
Bipolar	1	1	3	0.39	1	3	4	0.88
Anxiety	1	1	6	0.20	2	7	8	1.03
Agoraphobia	0	0	0	N/A	0	2	1	2.35
Obsessive Compulsive	0	0	0	N/A	0	0	0	N/A
Panic Disorder	0	0	0	N/A	0	1	1	1.17
Social Phobia	0	0	0	N/A	0	0	0	N/A
Post-Traumatic Stress Disorder	1	1	6	0.20	2	6	7	1.01
Externalizing Disorders	0	3	1	3.52	1	7	1	8.21 ^{**}
Attention Deficit	0	2	1	2.35	1	2	1	2.35
Hyperactivity Disorder								
Antisocial Personality Disorder	0	2	9	0.26 [*]	1	3	0	∞
Conduct Disorder	0	0	0	N/A	0	0	0	N/A

Significant Chi Square (2-sided):

* p<0.05,

** p<0.01; STAA, short-term abstinent alcoholics; LTAA, long-term abstinent alcoholics.

STAA, short-term abstinent alcoholics; LTAA, long-term abstinent alcoholics; NSAC, non-substance abusing controls; SD, standard deviation.

Table 4

Antisocial personality disorder (ASPD) measures previously reported in Fein and Fein 2012 in STAA and LTAA groups.

	LTAA	STAA	T	Sig.
Lifetime ASPD Symptom Count	7.35 (4.53)	6.74 (3.42)	0.53	0.601
Current ASPD Symptom Count	1.09 (1.73)	2.56 (2.41)	2.50	0.016*
California Psychological Inventory – Socialization Scale	17.43 (4.08)	18.81 (3.48)	1.28	0.209
Minnesota Multiphasic Personality Inventory – Psychopathic Deviance Scale	22.83 (5.80)	25.56 (5.53)	1.69	0.097

STAA, short-term abstinent alcoholics; LTAA, long-term abstinent alcoholics

Table 5

Regions in which LTAA have previously shown RSS differences when compared to NSAC (J. Camchong et al. 2012) on which current group analysis was based.

(A) NAcc				
Anatomy of region	L/R	x	y	Z
<i>Dorsolateral prefrontal cortex, BA 10</i>	L	-27	61	26
Caudate	L	-12	-1	15
	R	11	3	11
Anterior nucleus of thalamus	L	-10	-14	16
	R	10	13	14
Medial dorsal thalamus	L	-6	-25	5
	R	8	-21	7
Inferior parietal lobule, BA 40	L	-36	-54	59

(B) Subgenual ACC				
Anatomy of region	L/R	x	y	Z
<i>Dorsolateral prefrontal cortex, BA 8</i>	R	26	28	54
<i>Dorsolateral prefrontal cortex, BA 46</i>	R	52	34	20
Anterior nucleus of the thalamus	L	-12	2	12
	R	6	-2	10

Italics, regions in which LTAA had higher RSS than NSAC in previous paper (J. Camchong et al. 2012). LTAA, long-term abstinent alcoholics; RSS, resting state synchrony; NSAC, non-substance abusing controls; NAcc, nucleus accumbens; ACC, anterior cingulate cortex; BA, Brodmann area; L, left; R, right.

Table 6

Analysis of variance (ANOVA) results.

(A) Subgenual ACC

Anatomy of region	L/R	ANOVA	With polynomial contrast	p-value	STAA vs LTAA	Tukey p-value	STAA vs NSAC	Tukey p-value
			Linear	NSAC<STAA<LTAA	Quadratic			
Dorsolateral prefrontal cortex, BA 8 and 46	R		0.003		0.741	0.189		0.062
Anterior nucleus of the thalamus	L		0.011		0.435	0.046*		0.493
	R							

(B) NAcc

Anatomy of region	L/R	ANOVA	With polynomial contrast	p-value	STAA vs LTAA	Tukey p-value	STAA vs NSAC	Tukey p-value
			Linear	NSAC>STAA>LTAA	Quadratic			
Dorsolateral prefrontal cortex, BA 10	L		0.006		0.608	0.059		0.303
Caudate	L		0.004		0.814	0.087		0.187
	R							
Anterior nucleus of thalamus	L		0.001		0.072	0.001**		0.803
	R							
Medial dorsal thalamus	L		0.004		0.0003	0.000009***		0.089
	R							
Inferior parietal lobule, BA 40	L		0.005		0.455	0.386		0.034*

RSS, resting state synchrony; STAA, short-term abstinent alcoholics; LTAA, long-term abstinent alcoholics; NAcc, nucleus accumbens; L, left; R, right; ACC, anterior cingulate cortex; BA, Brodmann area

Table 7

Analysis of variance results showing no overall group differences in Intradimensional/Extradimensional Set Shift task performance

Behavioral Measure	NSAC (n = 23)		STAA (n = 27)		LTAA (n = 23)		F-value	p-value
	Mean z-score	SD	Mean z-score	SD	Mean z-score	SD		
Total number of Blocks completed successfully	0.07	0.67	-0.13	0.73	-0.16	0.95	0.56	0.57
Total number of trials completed on all attempted Blocks	-0.46	1.07	-0.27	0.85	-0.41	0.90	0.28	0.76
Adjusted total number of errors	0.05	0.60	-0.03	0.64	-0.11	0.84	0.29	0.75

NSAC, non-substance abusing controls; STAA, short-term abstinent alcoholics; LTAA, long-term abstinent alcoholics; SD, standard deviation.