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

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ABSTRACT

BACKGROUND: We previously reported that compared to controls, long-term abstinent alcoholics (LTAA) have increased resting state synchrony (RSS) of the executive 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: with longer abstinence there was higher RSS of the executive control network (NSAC<STAA<LTAA) and lower RSS of the appetitive drive network (NSAC>STAA>LTAA). We also found significant correlations between strength of RSS in these networks and (a) cognitive flexibility and (b) current antisocial behavior. DISCUSSION: Findings suggest that abstinent alcoholics have adaptive differences in RSS patterns depending on length of abstinence. Compared to normal controls, alcoholics with longer periods of abstinence have RSS patterns more different from controls than do alcoholics with shorter periods of abstinence. The differences from controls are characterized by (a) attenuated RSS within the appetitive drive network and (b) enhanced RSS within the executive control network.
**Introduction**

Alcohol dependence is 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 consequences (American Psychiatric Association 1994). Functional neuroimaging studies suggest that these aspects of alcohol dependence correspond to differences (from non-alcoholic controls) in brain function and organization within networks that mediate executive control of behavior (top-down) and appetitive drive toward consummatory behavior (bottom-up) (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 cues, crave, or consume alcohol, they show increased activity in appetitive drive regions, particularly in the nucleus accumbens (NAcc) (Myrick et al. 2004; Ihssen et al. 2011; Schacht et al. 2011). NAcc, a limbic region that mediates appetitive drive and behavior towards rewards, is presumably involved in the lack of flexibility necessary to generate new adaptive behavior and the inability to extinguish alcohol-related habits (Chen et al. 2011). It has been proposed that as alcohol use shifts from initial recreational use to a compulsive habit, there is a shift in the involvement of limbic regions, particularly from NAcc to caudate and putamen (Everitt and Robbins 2005; Vollstadt-Klein et al. 2010).

Functional differences from non-alcoholic controls within the executive control network have been identified in actively drinking alcoholics, particularly those associated with poor regulation of behavior and emotion, a core aspect of alcohol dependence (Fox et al. 2008; Berking et al. 2011). Dysfunctional emotion regulation in alcoholics (e.g., extremes in emotional responsiveness, 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**

Identifiable differences from normal controls in *abstinent* alcoholics may be related to abstinence length. The characteristics of top-down and bottom-up networks at different abstinence stages (short- vs long-term) may help identify brain mechanisms that support the cessation of drinking and the development of long-term abstinence.

**Short-term abstinence**

Studies examining top-down and bottom-up processing during short-term abstinence from alcohol have identified differences from controls in brain function and organization. An fMRI study using the monetary incentive delay task 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. An fMRI study on 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). Another fMRI study on male alcoholics abstinent for at least 7 days, found: (a) that alcoholics have significantly weaker DLPFC-NAcc synchrony than controls when viewing win versus loss feedback during a reinforcement learning task (Park et al. 2010) and (b) that the extent of DLPFC-NAcc synchrony attenuation was related to inability to control craving. Their results suggest that DLPFC-NAcc interaction plays an important role in modulating reward guided decision making as well as the ability to control craving.

**Long-term abstinence**

There is evidence from the task-evoked fMRI literature supporting the existence of compensatory mechanisms in alcoholics with longer periods of abstinence. 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. In addition, since short-term abstinent alcoholics 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 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 top-down and bottom-up functional differences in alcohol dependent samples vs. controls, the examination of resting state networks provides a different perspective on functional brain organization. Brain signal variations measured at rest characterized by low frequency fluctuations show temporal coherence across regions of the brain that comprise networks which represent the brain’s baseline activity (Beckmann et al. 2005). Resting state synchrony (RSS) allows us to investigate the organization of neural networks that likely impact the brain’s response to the environment (Biswal et al. 1997; Mennes et al. 2011).

Studies that have compared RSS between abstinent alcoholics and controls (Chanraud et al. 2011; Camchong et al. 2012; Pitel et al. 2012) have identified evidence for compensatory mechanisms during rest. Chaunraud 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). A
recent study by Pitel et al (2012) found that during rest, short-term abstinent alcoholics have negative correlation patterns between cerebellum and hippocampus while controls have a positive correlation pattern. During task performance, however, short-term abstinent individuals showed similar correlation patterns as controls with no difference in task performance levels. Pitel et al (2012) propose that short-term abstinent alcoholics have compensatory mechanisms in the level of synchrony between these regions to allow them to perform at control levels. Even though Pitel et al (2012) and Chaunraud 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 (executive control) or the bottom-up (appetitive drive) networks. A previous study from our group focused on examining resting state networks in the executive control (seeded in subgenual anterior cingulate) and the appetitive drive (seeded in NAcc) networks in long-term abstinent alcoholics (days abstinent: M=2888.78, SD=2848.14)(Camchong et al. 2012). We found enhanced synchrony in the executive control network and attenuated synchrony in the appetitive drive 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 are related to the behavioral control required to maintain abstinence (i.e., enhanced executive control and reduced drive).

Purpose of present study

The goal of this study was to investigate whether the differences from controls in long-term abstinent alcoholics in the strength of synchrony of executive 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 that the STAA will show: (1)
significant positive correlation between RSS involving executive control regions and performance on a task that assesses cognitive flexibility and (2) significant positive correlations between RSS involving appetitive drive and 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 (Camchong et al. 2012). All subjects were contemporaneously recruited from the island of Oahu (Table 1). Abstinent alcoholics were recruited through advertisements and fliers posted in various treatment programs including Alcoholic Anonymous meetings, and 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 (nicotine or caffeine excluded). All subjects’ substance use history was gathered using the Lifetime Drinking History instrument (Skinner and Sheu 1982), administered separately for alcohol (Table 2) and for each other substance used (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 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 (assessed by the C-DIS).

Imaging data acquisition

Resting functional magnetic resonance (fMRI) data were collected using a twelve-channel head coil on a Siemens TimTrio 3.0T scanner (Siemens Medical Solutions, Erlangen, Germany) located at Queen’s Medical Center in Honolulu (Camchong et al. 2012; Camchong et al. 2012). Subjects were instructed to lay motionless in the scanner with their eyes closed. The imaging sequence was a gradient-echo spiral in/out sequence (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) (Noll et al. 1995; Glover and Law 2001). 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 and -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. First three volumes were discarded from data analysis to ensure magnetization reached steady state.

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

All imaging data were preprocessed using AFNI (Analysis of Functional NeuroImages (Ward 2000)) and FMRIB Software Libraries (FSL; FMRIB, Oxford, United Kingdom)(Camchong et al. 2012; Camchong et al. 2012). 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 (Camchong et al. 2011; Camchong et al. 2012; Camchong et al. 2012). 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). The trend in
group differences, seems to be driven by differences between STAA and LTAA (p=0.061), while
NSAC did not show significant differences when compared to STAA (p=0.840) or LTAA
(p=0.219).

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).
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 transformation matrices were used to
register each individual’s preprocessed and denoised fcMRI data to MNI standard space for
group analysis.

Resting state individual-level analysis

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;
(Camchong et al. 2012; Camchong et al. 2012)). 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 (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). Mean z-scores (representing strength of RSS with the seed) within clusters in Table 5 were extracted from individual PE maps. An analysis of variance (ANOVA; SPSS) was conducted using these extracted mean z-scores 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 (Table 5).

Behavioral task

All subjects were administered the intradimensional/extradimensional set shift (IED) task (Cambridge Cognition 2006) (Camchong et al. 2012) to evaluate cognitive flexibility by requiring subjects to change a learned response when response contingencies changed. During the task, subjects learn which of two stimuli is correct via feedback. Unbeknownst to subjects, the rules change after six correct responses. Rule changes are intra-dimensional (based on stimuli shape) or extra-dimensional (based on white lines next to stimuli shape). Correlates of RSS

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 appetitive drive 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 task performance in the LTAA group, we investigated this same relationship in STAA. Second, our group recently reported that while antisocial disposition (antisocial thinking) was elevated in both STAA and LTAA when compared to non-substance abusing controls, only STAA showed elevated antisocial behavior (current symptom count of antisocial personality disorder - ASPD), whereas LTAA did not differ from non-substance abusing controls (Fein and Fein 2012). Based on this observation, we investigated two specific correlations between ASPD current symptom count and average RSS strength in STAA. First, because of the important role of appetitive drive regions in antisocial behavior (Raine et al 2010; Finger et al 2012; Buckholtz et al 2010; Bjork et al 2012), particularly in alcoholics (Oberlin et al 2012), we investigated whether STAA exhibited a positive association between current ASPD symptoms (reflective of current antisocial behavior) and RSS of appetitive drive regions. Second, because fMRI studies associated frontal lobe dysfunction with inhibition of antisocial behavior (Brower et al 2001; Motzkin et al 2011), we investigated whether STAA showed a negative correlation between current ASPD symptom counts and RSS of executive control regions.

**Results**

To examine RSS differences between groups and linear trends, we conducted an ANOVA with polynomial contrasts within clusters previously found to be different between LTAA and NSAC. We found the following trend effects of group in clusters examined: *Significant linear trend of higher RSS of executive control regions with predetermined seeds.* There were significant linear group differences in RSS between DLPFC and the NAcc (ANOVA: F=4.174, p=0.019, linear trend significance: p=0.006) and sgACC (ANOVA: F=4.854, p=0.011, linear
trend significance: p=0.003) seeds when contrasting NSAC, STAA, and LTAA
(NSAC<STAA<LTAA; Table 5, Figures 2 and 3).

**Significant linear trend of lower RSS of appetitive drive regions with predetermined seeds.** There were significant linear group differences in RSS between the NAcc and sgACC seeds and regions previously found to be significantly lower RSS in LTAA than NSAC (NSAC>STAA>LTAA) (Camchong et al. 2012). This pattern was present when examining appetitive drive network synchrony between: (a) NAcc and inferior parietal lobule (Figure 4B; ANOVA: F=4.532, p=0.014, linear trend significance: p=0.005), (b) NAcc and bilateral caudate (Figure 4B; ANOVA: F=4.384, p=0.016; linear trend significance: p=0.004), (c) NAcc and bilateral anterior nucleus of the thalamus (Figure 4B; ANOVA: F=7.744, p=0.001, linear trend significance: p=0.001), and (d) sgACC and anterior nucleus of the thalamus (Figure 5; ANOVA: F=3.736, p=0.029, linear trend significance: p=0.011).

**Linear and non-linear effects in RSS.** There were significant group differences (ANOVA: F=11.658, p=0.000043) with significant linear (p=0.004) and nonlinear (p=0.0003) trends 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 (Camchong et al. 2012)), STAA did not. STAA had significantly higher RSS between these regions when compared to LTAA.

**Behavioral task performance**

To examine whether groups differed in cognitive flexibility, we compared IED task performance. ANOVA results showed no significant differences in IED task performance in: number of blocks completed successfully (F=0.562, p=0.572), number of trials needed to complete a block (F=0.276, p=0.760), or adjusted total number of errors across groups (F=0.293, p=0.747) (Table 6).

**RSS behavioral correlates in STAA group**
The STAA group showed a strong trend toward a positive correlation between IED task 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 task performance. STAA also had a significant positive correlation between the number of current ASPD symptoms and average RSS strength within the appetitive drive network (Spearman’s Rho=0.411, p=0.033). As hypothesized, there were no significant correlations between average RSS in the appetitive drive network and MMPI’s Psychopathic Deviance subscale or Socialization scores of the California Psychological Inventory.

**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) (Camchong et al. 2012) could be identified in short-term abstinent alcoholics (STAA). We found significant abstinence duration ordered RSS effects in both networks: higher RSS (NSAC < STAA < LTAA) of top-down executive control regions (i.e. DLPFC), and lower RSS (NSAC > STAA > LTAA) of bottom-up appetitive drive 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 appetitive drive network was correlated with the number of current antisocial symptoms.

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

We reported that STAA also show higher RSS between DLPFC and both seeds (NAcc and sgACC) when compared to NSAC, but to a lesser degree than LTAA (Figures 2 and 3). Based on current and previous results (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 individuals within the STAA group with higher average strength of RSS within regions of the executive control network had better cognitive flexibility. A recent study by Chanraud et al (2012) that examined both strength of RSS and task-related brain activation during working memory in abstinent alcoholics (>30 days abstinent), reported that alcoholics have increased DLPFC engagement both during rest as well as when performing a working memory task when compared to healthy controls. Increased RSS between executive control regions associated with better executive functioning may be present even before the onset of alcohol abuse (Wetherill et al 2012). Wetherill and colleagues (2012) reported lower RSS between executive control regions in young substance-naïve individuals with a family history of alcoholism when compared to controls, a difference that was correlated with poor executive functioning. They suggest that lower RSS between executive control regions may be a preexisting neurobiological marker that increases vulnerability to alcohol use disorders via poor executive functioning. The etiology of RSS differences in alcoholics cannot be fully addressed in the current cross-sectional study. Our results support two alternative propositions: (1) there is selective survivorship, in which only STAAs with enhanced RSS of executive control regions and attenuated RSS of appetitive drive regions reach long-term abstinence or (2) the pattern of RSS in executive control and appetitive drive regions changes with long-term abstinence. Aside from etiology, current correlational results do suggest that enhanced RSS of executive control regions is related to better executive control performance and that lack of attenuation of RSS of appetitive drive regions is related to behavior ruled by appetitive drive.

Ordered effects of lower RSS during abstinence in alcoholics

We found abstinence duration ordered effects of decreasing RSS between appetitive drive regions when contrasting NSAC, STAA and LTAA (NSAC>STAA>LTAAS) (Figures 4 and 5). Similar to LTAA, STAA also show lower RSS in appetitive drive regions when compared to
NSAC, but to a lesser degree than LTAA. Based on current and previous results (Camchong et al. 2012), we propose that abstinent alcoholics disengage interactions of regions known to be part of the appetitive drive network in order to avoid the probability of falling back into relapse. Importantly, this disengagement may be a function of abstinence length.

Engagement of appetitive drive regions varies depending on the stage of alcohol dependence. Studies have reported an increased engagement of appetitive drive 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 appetitive drive regions (Myrick et al. 2004; Ihssen et al. 2011; Schacht et al. 2011). Our results on short- and long-term abstinent alcoholics provide evidence that the engagement of appetitive drive regions is attenuated during the course of abstinence (when appetitive behaviors are inhibited) to minimize organized interaction of regions that process appetitive drive and avoid relapse. This attenuation seems to be stronger with longer length of abstinence.

Our findings of higher current antisocial behavior in short-term abstinence than in long-term abstinence (Table 3) reiterates our previous reports (Fein and Fein 2012). While most studies in the literature have reported an association between antisocial behavior and attenuated activity or synchrony of executive control regions (Muller et al. 2003; Yang et al. 2008; Motzkin et al. 2011; Pujol et al. 2011; Juárez et al. 2012), there are a few studies that have reported that antisocial behavior is also associated with heightened activation or synchrony of appetitive drive regions (Buckholtz et al. 2010; Bjork et al. 2012). Our current finding of a positive association between RSS within the appetitive drive network and current antisocial symptoms in STAA is novel, suggesting a link between current antisocial behavior
and enhanced RSS within brain regions known to process reward. It is important to note that while antisocial behavior was correlated with average appetitive drive network RSS, measures of antisocial disposition (i.e. MMPI’s Psychopathic Deviance subscale and California Psychological Inventory Socialization Scale), which do not differ between short- and long-term abstinent alcoholics (Fein and Fein 2012), were not correlated.

A limitation of the current study is its cross-sectional design, which does not assess changes over time. 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 within individuals with duration of abstinence. We note that LTAA started drinking at a younger age than STAA. We do not believe, however, that this had a crucial effect on the RSS differences observed, because (1) age when alcohol consumption reached heavy use did not differ between STAA and LTAA (Table 2), and (2) if the RSS findings were strongly determined by age at first drink, we would expect the results to be opposite to what we observed (lower executive RSS and higher appetitive RSS in LTAA vs. STAA). We would expect this because a younger age at first drink is a potential marker for more severe alcoholism. If such an effect were active in the current study, we believe it most likely would have attenuated the RSS differences found. We also note that, while STAA and LTAA did not differ in lifetime mood symptoms, STAA had more current mood symptoms than LTAA. These current symptom findings may either reflect changes that take place over long-term abstinence or may reflect a survivor effect, wherein individuals with fewer current mood symptoms are more likely to survive to very long-term abstinence. In either case, these symptom differences may have an impact on our observed RSS differences (Liu et al 2012; Greicius et al 2007), and warrants further examination in longitudinal studies that can disentangle change vs. selective survivorship effects.
In conclusion, we believe that current results provide evidence for short-term abstinent alcoholics having a different pattern strength of appetitive drive and executive 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 RSS strength in these networks with duration of abstinence so that alcoholics with longer abstinence have (a) enhanced synchrony of executive control regions and (b) attenuated synchrony of appetitive drive regions. In addition, (a) enhanced synchrony between executive control regions was associated with better cognitive flexibility and (b) lack of disengagement of synchrony between appetitive drive 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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References


Figure Legends

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 (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 (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 (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 (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.

**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 task 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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>STAA</th>
<th>LTAA</th>
<th>NSAC</th>
<th>STAA vs LTAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (yrs)</td>
<td>49.27</td>
<td>48.46</td>
<td>47.99</td>
<td>0.26</td>
</tr>
<tr>
<td>Education, (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject</td>
<td>14.56</td>
<td>13.22</td>
<td>14.74</td>
<td>3.45</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>--</td>
</tr>
<tr>
<td>Nicotine Use History, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current, n (%)</td>
<td>9</td>
<td>11</td>
<td>3</td>
<td>3.45</td>
</tr>
<tr>
<td>Additional Substances Used</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine, n (%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4.35</td>
</tr>
<tr>
<td>Methamphetamine, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Marihuana, n (%)</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>4.35</td>
</tr>
</tbody>
</table>

*p<0.05

Tukey Post-Hoc tests 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).

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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>STAA (n = 27)</th>
<th>LTAA (n = 23)</th>
<th>t</th>
<th>Sig (2-tailed)</th>
<th>Effect Size Partial Eta²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age started drinking, (yrs)</td>
<td>18.07</td>
<td>5.42</td>
<td>15.17</td>
<td>4.12</td>
<td>4.14</td>
</tr>
<tr>
<td>Age when consumption reached heavy use (yrs)</td>
<td>26.73</td>
<td>1.83</td>
<td>23.08</td>
<td>1.91</td>
<td>1.91</td>
</tr>
<tr>
<td>Proportion of 1st degree relatives who are problem drinkers (total number/number of relatives)</td>
<td>0.31</td>
<td>0.30</td>
<td>0.33</td>
<td>0.27</td>
<td>0.05</td>
</tr>
<tr>
<td>Average Dose (Lifetime; standard number of drinks per month)</td>
<td>193.88</td>
<td>250.57</td>
<td>188.51</td>
<td>163.03</td>
<td>0.11</td>
</tr>
<tr>
<td>Dose During Peak Use (number of drinks per month)</td>
<td>378.84</td>
<td>451.05</td>
<td>328.65</td>
<td>258.78</td>
<td>0.24</td>
</tr>
<tr>
<td>Length of Abstinence (number of days)</td>
<td>72.59</td>
<td>18.36</td>
<td>2888.78</td>
<td>2848.14</td>
<td>25.51</td>
</tr>
</tbody>
</table>

*p<0.05  
*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 (Camchong et al. 2012)

<table>
<thead>
<tr>
<th>Psychiatric Diagnoses</th>
<th>Current Diagnoses Count</th>
<th>Lifetime Diagnoses Count</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NSAC (n=23)</td>
<td>LTAA (n=23)</td>
<td>STAA (n=27)</td>
</tr>
<tr>
<td>Internalizing disorders</td>
<td>2</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Mood</td>
<td>2</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Manic Episode</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hypomaniac</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Major Depressive Disorder</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Bipolar</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Obsessive Compulsive</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Post-Traumatic Stress Disorder</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Externalizing Disorders</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Antisocial Personality Disorder</td>
<td>0</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Significant Chi Square (2-sided): *p<0.05, **p<0.01; 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.

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

STAA, short-term abstinent alcoholics; LTAA, long-term abstinent alcoholics
Table 5. Analysis of variance (ANOVA) results.

(A) Subgenual ACC

<table>
<thead>
<tr>
<th>Anatomy of region</th>
<th>RSS Mean (SD)</th>
<th>ANOVA With polynomial contrast p-value</th>
<th>STAA vs LTAA Tukey p-value</th>
<th>STAA vs NSAC Tukey p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NSAC</td>
<td>STAA</td>
<td>LTAA</td>
<td>Linear NSAC&gt;STAA=LTAA</td>
</tr>
<tr>
<td>Right dorsolateral prefrontal cortex, BA 8 and 46</td>
<td>0.07 (0.20)</td>
<td>0.20 (0.29)</td>
<td>0.30 (0.22)</td>
<td>0.003</td>
</tr>
<tr>
<td>Bilateral anterior nucleus of the thalamus</td>
<td>0.14 (0.31)</td>
<td>0.31 (0.35)</td>
<td>0.37 (0.23)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

(B) NAcc

<table>
<thead>
<tr>
<th>Anatomy of region</th>
<th>RSS Mean (SD)</th>
<th>ANOVA With polynomial contrast p-value</th>
<th>STAA vs LTAA Tukey p-value</th>
<th>STAA vs NSAC Tukey p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NSAC</td>
<td>STAA</td>
<td>LTAA</td>
<td>Linear NSAC&gt;STAA=LTAA</td>
</tr>
<tr>
<td>Left dorsolateral prefrontal cortex, BA 10</td>
<td>0.23 (0.28)</td>
<td>0.32 (0.25)</td>
<td>0.46 (0.28)</td>
<td>0.006</td>
</tr>
<tr>
<td>Bilateral Caudate</td>
<td>0.73 (0.36)</td>
<td>0.61 (0.28)</td>
<td>0.45 (0.34)</td>
<td>0.004</td>
</tr>
<tr>
<td>Bilateral anterior nucleus of the thalamus</td>
<td>0.54 (0.32)</td>
<td>0.52 (0.30)</td>
<td>0.23 (0.30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Bilateral medial dorsal thalamus</td>
<td>0.54 (0.29)</td>
<td>0.68 (0.26)</td>
<td>0.28 (0.32)</td>
<td>0.004</td>
</tr>
<tr>
<td>Left inferior parietal lobule, BA 40</td>
<td>0.54 (0.29)</td>
<td>0.36 (0.28)</td>
<td>0.28 (0.32)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

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

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

NSAC, non-substance abusing controls; STAA, short-term abstinent alcoholics; LTAA, long-term abstinent alcoholics; SD, standard deviation.
Figure 1.

(A) Nucleus Accumbens  (B) Subgenual ACC
Figure 2.
Figure 3.

(A) Executive Control: RSS between sgACC seed and DLPFC
NSAC<STAA<LTA

(B) Intermediate RSS in STAA

[1] Right DLPFC
Figure 4.

(A) Reward: tSS between NAcc seed and reward processing regions

NSAC > STAA > LTAA

(B) Mean z-scores

Figure 5.

(A) Reward: RSS between sgACC seed and AN-Thal
NSAC > STAA > LTAA

(B) Intermediate RSS in STAA

[1] Bilateral AN-Thal

[1] Bilateral AN-Thal

RSS with sgACC - Mean z-scores

NSAC  STAA  LTAA

z=12

0.0  0.2  0.4  0.6  0.8  1.0
Figure 6.

Executive control RSS correlated with cognitive flexibility in STAA

Pearson's $R = 0.403$, $p = 0.037$
Spearman's $\rho = 0.368$, $p = 0.059$