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Resting state synchrony in long-term abstinent alcoholics: Effects of a current major depressive disorder diagnosis

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Abstract

Alcoholism is characterized by a lack of control over an impulsive and compulsive drive toward excessive alcohol consumption despite significant negative consequences; our previous work demonstrated that successful abstinence is characterized by decreased resting-state synchrony (RSS) as measured with functional magnetic resonance imaging (fMRI), within appetitive drive networks and increased RSS in emotion regulation and inhibitory executive control networks. Our hypothesis is that LTAA (Long-Term Abstinent Alcoholics) with a current major depressive disorder (MDD) drank primarily to deal with the negative affect associated with their MDD and not because of a heightened externalizing diathesis (including heightened appetitive drive), and consequently, in achieving and maintaining abstinence, such individuals would not exhibit the RSS adaptations characteristic of pure alcoholics. We studied 69 NSAC (Non Substance Abusing Controls) and 40 LTAA (8 with current MDD, 32 without a current MDD) using resting-state fMRI and seed based connectivity analyses. In the inhibitory executive control network (nucleus accumbens vs. left dorsolateral prefrontal cortex), LTAA with a current MDD showed increased synchrony compared to NSAC. In the emotion regulation executive control network (subgenual anterior cingulate cortex vs. right dorsolateral prefrontal cortex), LTAA with current MDD did not show increased RSS. In the appetitive drive networks (nucleus accumbens vs. aspects of the caudate nucleus and thalamus), LTAA with a current MDD did not show a reduction of RSS compared to NSAC, but LTAA without a current MDD did. These results suggest different

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Contributors

All authors materially participated in the reported research. Andrew Stenger designed the imaging protocols and collected the resting state fMRI data, Jazmin Camchong designed the resting-state functional connectivity analysis and analyzed all data in the primary analysis, Valerie Cardenas contributed to the secondary analysis (alcoholics with vs. without major depression) and writing of the manuscript, and George Fein conceived the study, contributed to writing, and had overall scientific responsibility. All study authors have approved the final article.

Conflict of interest

There are no conflicts of interest to report for any author.

pathways to their alcohol dependence in LTAA with vs. without a current MDD, and different patterns of brain activity in long-term abstinence, suggesting different treatment needs.

Keywords

fMRI; Executive control network; Appetitive drive network; Functional connectivity; Major depressive disorder; Alcoholism

1. Introduction

In a cross-sectional study on the Island of Oahu, we recently showed that 14.5% of middle-aged Long-Term (>1.5 years) Abstinent Alcoholics (LTAA, $n = 110$) had a current Major Depressive Disorder (MDD) diagnosis, over five times the rate of 2.4% in age and gender comparable Non-Substance Abusing Controls (NSAC, $n = 82$) (G. Fein, 2013). In 2007, we found a comparable difference in analogous groups in Northern California (52 LTAA vs. 48 NSAC), with a current MDD diagnosis present in 4.2% of NSAC vs. 19.2% of LTAA (Di Sclafani, Finn, & Fein, 2007). We are hypothesizing that the bulk of **current** MDD diagnoses in LTAA reflects depression independent of – rather than secondary to – the substance use disorder (SUD). Were MDD secondary to the SUD, one would expect the majority of MDDs to have resolved over multiple years of abstinence. We are proposing that the majority of LTAA with a **current** MDD had a primary depression that they medicated with alcohol (often with drugs also). The combined burden of an MDD and alcohol dependence (sometimes also with drug dependence) drove such individuals to formal treatment or 12-step recovery, where they have been successful for multiple years in maintaining abstinence from alcohol and drugs. However, they have not been particularly successful in dealing with their MDD. Were their efforts to deal with their MDD successful, one would expect the disorder to be in remission.

In the current manuscript, we are revisiting resting-state functional magnetic resonance imaging (rs-fMRI) data for LTAA, comparing LTAA with vs. without a current MDD. For simplicity, we restricted this re-examination of data to LTAA without a concurrent lifetime drug use disorder ($n = 40$).

Alcoholism is characterized by a lack of control over an impulsive and compulsive drive toward excessive alcohol consumption despite significant negative consequences. These impulsive and compulsive behaviors are related to the reorganization of brain functional networks with repeated high level alcohol exposure (Kalivas, 2008; Mameli & Luscher, 2011), resulting in increased synchrony in appetitive drive networks and decreased synchrony in executive control networks (Volkow, Wang, Tomasi, & Baler, 2013). Using the analogy of a car, the alcoholic is primed to shoot out into a dangerous intersection (continued abusive drinking despite accumulating major consequences) because the motor is idling way too fast (craving is easily elicited by alcohol-related stimuli), and the brakes are faulty (they have limited inhibitory control and ability to regulate emotions). With rs-fMRI, we have shown adaptive changes in brain network resting state synchrony (RSS) in LTAA that reverse the network synchrony differences that were associated with the development of alcoholism. LTAA compared to NSAC show lower synchrony in appetitive drive networks

and higher synchrony in the inhibitory executive control network and the emotion regulation executive control network (J. Camchong, A. Stenger, & G. Fein, 2013a), with similar, although attenuated, effects in short-term (6–15 week) abstinent alcoholics (STAA) (J. Camchong, V. A. Stenger, & G. Fein, 2013b). Our hypothesis is that LTAA with a current MDD would not exhibit heightened appetitive drive toward alcohol consumption as a central engine underlying their alcoholism. Our hypothesis is that they drank primarily to deal with the negative affect associated with their MDD. Consequently, the adaptive compensatory rs-fMRI changes in such individuals would not include a lowering of RSS in the appetitive drive network. Moreover, given their current problems with depression, we hypothesize that such individuals would not exhibit increased RSS in the emotion regulation executive control network, but would only exhibit increased RSS within the inhibitory executive control network.

2. Methods

2.1. Participants (see Table 1)

A total of 109 individuals, 35–60.9 years of age were recruited from the Honolulu area by postings at AA meetings, community and treatment centers and participant referrals. LTAA (n = 40, 17 women and 23 men) met DSM-IV criteria for lifetime alcohol dependence (American Psychiatric Association, 1994), but not for lifetime abuse or dependence on any other drugs of abuse (other than nicotine or caffeine). LTAA were between 35.0 and 58.9 years of age (mean = 48.8 years), and were abstinent from alcohol and drugs for between 75.6 and 1678.6 weeks (mean = 367.9 ± 386.6 weeks). NSAC (n = 69, 34 women and 35 men) were between 35.3 and 60.9 years of age (mean = 48.6 years). NSAC had a lifetime drinking average of less than 30 standard drinks per month with no periods of drinking more than 60 drinks per month, and no lifetime history of alcohol or substance abuse or dependence. A standard drink was defined as 12 oz beer, 5 oz of wine or 1.5 oz of liquor.

Exclusion criteria for all groups were: 1) significant history of head trauma or cranial surgery, 2) history of diabetes or stroke, 3) history of significant neurological disease, 4) laboratory evidence of hepatic disease, 5) clinical evidence of Wernicke-Korsakoff syndrome, and 6) lifetime or current diagnosis of schizophrenia or schizophreniform disorder as determined by the computerized Diagnostic Interview Schedule (c-DIS, see below). After a complete description of the study to the subjects, written informed consent was obtained. As presented in our other publications (George Fein, 2013; G Fein, 2015), psychiatric comorbidity was very high in the LTAA sample.

2.2. Procedures

NSAC were asked to abstain from alcohol for 24 h prior to any lab visit. A breathalyzer test (Intoximeters, Inc., St. Louis, MO) was administered to all participants and a 0.00 alcohol concentration was required before proceeding. A rapid oral fluid drug screen test (Innovacon Inc., San Diego, CA) for THC, methamphetamines, cocaine, opioids, and PCP was also administered to all participants, with a negative result required for participation. Participants were compensated for their time and travel expenses. The data presented here were from the clinical and psychiatric assessments and the MRI session. The study was reviewed and

approved by an independent human subjects research review committee (E&I Review Services, LLC, Corte Madera, CA).

2.3. Alcohol, substance and nicotine use measures

Participants were interviewed on their lifetime use of alcohol and each drug of abuse that they had taken (including nicotine) using the timeline follow-back methodology (Skinner & Allen, 1982; Skinner & Sheu, 1982; Sobell & Sobell, 1992), with criteria for abuse or dependence gathered using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV) (Grant et al., 2003). For the purpose of the current study, these procedures yielded average and peak dose of alcohol, and abstinence duration.

2.4. MDD diagnoses

The computerized Diagnostic Interview Schedule (c-DIS) (Bucholz et al., 1991; Erdman et al., 1992; Levitan, Blouin, Navarro, & Hill, 1991; Robins LN, Bruckholz, & Compton, 1998) was administered to all participants by a research associate who asked the c-DIS questions and helped navigate through the c-DIS decision tree. This also allowed the research associate to compare the participants' answers to their phone screen and other volunteered information. The c-DIS assessed for the following current and lifetime diagnoses in the mood, anxiety, and externalizing domains: bipolar disorder, dysthymia, hypomania, mania, MDD, agoraphobia, compulsive disorder, obsessive disorder, panic disorder, post-traumatic stress disorder (PTSD), social phobia, conduct disorder and antisocial personality disorder.

2.5. Imaging data acquisition

Imaging acquisition and pre-processing sections follow the same protocol described in our previous study of long-term abstinent alcoholics (Camchong, Stenger, & Fein, 2013a). Resting state functional connectivity magnetic resonance imaging (fcMRI) 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 & Law, 2001; Noll, Cohen, Meyer, & Schneider, 1995). Images were reconstructed using a custom gridding reconstruction program with a field map based off resonance correction (Jackson, Meyer, Nishimura, & Macovski, 1991; Noll, Meyer, Pauly, Nishimura, & Macovski, 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. The fcMRI scan acquired a total of 123 vol with 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 (TE = 31 ms) for field map measurement and was excluded from fcMRI analysis.

A high-resolution T1-weighted structural image was 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.

2.6. fcMRI data preprocessing

All imaging data was preprocessed using AFNI (Analysis of Functional NeuroImages) and FSL (FMRIB Software Libraries; Oxford, United Kingdom) as in our previous paper (Camchong et al. 2013a). Preprocessing consisted of: dropping first 3 TRs to account for magnet field homogenization; slice time correction; three-dimensional motion correction (AFNI: 3dvolreg); skull stripping; temporal despiking; spatial smoothing (full width at half maximum = 6 mm); mean-based intensity normalization; temporal band-pass filtering (0.009–0.1 Hz); and linear and quadratic detrending. Three dimensional motion correction calculations provided motion correction parameters for each participant for translation in the x, y and z planes, and rotation (pitch, roll, and yaw). Probabilistic independent component analysis was conducted for each individual to denoise individual data by removing components that represented noise such as head motion (i.e. “rim-like” artifacts around the brain), scanner artifacts (i.e. slice dropouts, high-frequency noise, field inhomogeneities), and physiological noise (i.e. respiration, cardiac frequencies, white matter, cerebrospinal fluid fluctuations). Noise components were selected by spatial and temporal characteristics detailed in the MELODIC (FSL) manual (<http://fmrib.ox.ac.uk/fslcourse/lectures/melodic.pdf>), based on Kelly et al. (2010) and applied in our previous papers (Camchong, MacDonald, Bell, Mueller, & Lim, 2011; Camchong, MacDonald, Nelson, et al., 2011).

Image registrations were conducted with FSL-FLIRT (FMRIB’s Linear Image Registration Tool) which uses an automated linear (affine) registration (Jenkinson, Bannister, Brady, & Smith, 2002). First, each individual’s preprocessed and denoised fcMRI data was registered to the individual’s high-resolution T1-weighted structural image (with 6 degrees of freedom), generating a transformation matrix file. The high-resolution T1-weighted structural image was then registered to the standard Montreal Neurological Institute (MNI-152) brain (with 12 degrees of freedom), generating 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 prior to group analysis.

2.7. Region of interest selection and seed generation

We previously reported significant differences between LTAA and NSAC in resting state networks generated with seeds in the nucleus accumbens (NAcc) and in the subgenual anterior cingulate cortex (sgACC) (Camchong et al., 2013a). NAcc was selected because of its key role in processing the rewarding effects of alcohol or drugs (Everitt & Robbins, 2005; Koob & Le Moal, 1997). Repeated exposure to alcohol or drugs has been shown to generate long-lasting synaptic changes in the nucleus accumbens, re-organizing its connections within the appetitive drive network (Lee & Dong, 2011). SgACC was selected because of its key role in exerting control on emotion (A. M. Kelly et al., 2009), particularly in alcoholics (Salloum et al., 2007). 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). The present study used these same

regions, NAcc and sgACC, as seeds (3.5 mm radius) to generate the appetitive drive and executive control networks respectively (Camchong et al., 2013a).

2.8. Resting state individual-level analysis

For each participant and for each seed (sgACC and NAcc), an average time-series was extracted (3dROIstats, AFNI). A multiple regression analysis (3dfim+, AFNI) on the denoised data was performed between the extracted average time-series from the seed and all voxels in the brain. This analysis generated a correlational map with a correlation coefficient for each voxel, for each individual, for each seed. Correlation coefficients (r) were transformed to standardized z values (3dcalc, AFNI). All voxels in the resulting standardized z maps showed the degree of positive or negative correlations with the corresponding seed averaged time-series for each seed for each participant. For the analyses in the current study, we examined group differences within the (appetitive drive and executive control) clusters in which we previously found RSS differences between LTAA and NSAC (Camchong et al., 2013a). For the appetitive drive network, for the NAcc seed, clusters include the Caudate, Anterior Nucleus of the Thalamus, and the Medial Dorsal Thalamus; for the sgACC seed, only the medial dorsal thalamus showed a significant cluster.

2.9. Statistical analysis

Data were analyzed using the General Linear Model procedure in SPSS. Before examining RSS differences between LTAA with vs. without a current MDD, the RSS within the executive control and appetitive drive networks were compared between the larger LTAA and NSAC samples (displayed in Figs. 1 and 2) to confirm that the differences in executive control and appetitive drive RSS we saw in our initial study (Camchong et al., 2013a) are present in the larger samples of which the earlier study was a subset. Subsequently, the primary hypothesis under investigation was tested by comparing results of two MANOVAs. Each MANOVA had as its dependent variables the cluster correlations within the network under study (executive control or appetitive drive), with Group as the fixed effect. In one set of MANOVAs, the Group effect compared NSAC to LTAA without a current MDD diagnosis. In the other MANOVAs, the Group effect compared NSAC to LTAA with a current MDD diagnosis. Follow-up analyses broke LTAA without a current MDD diagnosis into LTAA without a lifetime MDD diagnosis and LTAA with a lifetime MDD diagnosis in remission.

We also examined alcohol measures (dose and abstinence duration) as covariates in comparisons among the LTAA, first examining subgroup by covariate interaction effects to test for the appropriateness of the analysis of covariance (ANCOVA).

3. Results

Table 1 presents demographic and alcohol use, average age of MDD symptom onset, and presence of psychiatric comorbidities broken out by NSAC and the three subgroups of LTAA (no Lifetime MDD or MDDN, Lifetime MDD in Remission or MDDR, and Current MDD or MDDC). Comparisons are presented between NSAC vs. the combined LTAA samples, and among the three LTAA sub-samples. The table shows that NSAC and LTAA

were comparable in age, while LTAA had less education than NSAC and a higher family history density of alcohol problems than NSAC. The table also shows the dramatic differences between NSAC and LTAA in alcohol use measures consistent with LTAA having chronic AUDs, and in the presence of psychiatric comorbidities (all $p < 0.05$, except for current externalizing disorders with $p = 0.10$). The LTAA subgroups did not differ on any alcohol use measure, showing that any differences we find below in rs-fMRI network RSS are not a function of differences in alcohol intake or abstinence duration. In addition, the LTAA subgroups did not differ on the presence of anxiety or externalizing disorders.

Enhanced executive control RSS in abstinent alcoholics described above (Camchong et al., 2013a) is identified in what we believe are two distinct networks (illustrated in Fig. 1). Compared to NSAC, LTAA showed enhanced RSS (yellow line) between bilateral NAcc (yellow clusters) and left DLPFC (red cluster), regions known to be involved in reward processing (NAcc) and inhibitory control (left DLPFC; (Kadota et al., 2010; Nathaniel-James, 2002)); ongoing enhancement of inhibitory control over reward processing may help alcoholics to maintain abstinence. Additionally, when compared to NSAC, abstinent alcoholics also showed enhanced RSS (green line) between sgACC (green cluster) and right DLPFC (red cluster), regions known to be involved in emotion regulation (sgACC) and emotional judgments (right DLPFC) (Grimm et al., 2008); ongoing enhancement of emotion regulation and judgment may also mediate successful abstinence in alcoholics. Reduced appetitive drive RSS in abstinent alcoholics described above is identified in a single network. Compared to NSAC, LTAA showed lower RSS between the caudate and thalamus, limbic regions involved in appetitive drive, with both the NAcc and sgACC seeds (illustrated in Fig. 2). Lower synchrony in the appetitive drive network may contribute to successful maintenance of abstinence. The coordinates of the regions shown in Figs. 1 and 2 corresponding to the DLPFC, caudate nucleus, and thalamus can be found in Table 2A of Camchong et al., 2013a.

3.1. LTAA vs NSAC

Confirming our earlier findings in a subsample of the current study (Camchong et al., 2013a), LTAA showed higher average executive control RSS than NSAC, averaged across the inhibitory control and emotion regulation aspects of executive control (Fig. 1, $F_{1,107} = 7.95$, $p = 0.006$, $es = 6.9\%$), and lower average appetitive drive RSS than NSAC (Fig. 2, $F_{1,107} = 9.10$, $p = 0.003$, $es = 7.8\%$). The group effects within the executive control and within appetitive drive networks did not differ across the clusters (Wilks' $\lambda_{2,106} = 0.99$, $p = 0.79$, $es = 0.5\%$, and Wilks' $\lambda_{3,105} = 0.96$, $p = 0.31$, $es = 3.4\%$).

3.2. LTAA-MDDN vs. LTAA-MDDR

There were no differences between LTAA-MDDN and LTAA-MDDR in executive control RSS ($p = 0.956$) or appetitive drive RSS ($p = 0.508$), and these two groups were merged together to represent LTAA without a current MDD diagnosis and labeled as LTAA-MDDNR for the remaining analyses. Figs. 3–5 present LTAA-MDDN and LTAA-MDDR separately, showing that they are close to identical on the dependent variables (the RSS measures for the inhibitory control, emotion regulation, and appetitive drive RSS measures).

3.3. Executive control RSS as related to a current MDD diagnosis

Comparing executive control RSS in LTAA-MDDNR vs. NSAC showed trends toward higher RSS in the inhibitory control executive network (Fig. 3; $F_{1,99} = 2.66$, $p = 0.10$, $es = 2.6\%$), and the emotion regulation executive network (Fig. 4; $F_{1,99} = 3.60$, $p = 0.06$, $es = 3.5\%$), with no difference between the Right DLPFC clusters ($es = 0.0\%$). Comparing the inhibitory control executive network RSS in LTAA-MDDC vs. NSAC showed higher RSS in LTAA-MDDC vs. NSAC (Fig. 3; $F_{1,75} = 5.97$, $p = 0.017$, $es = 7.4\%$). In contrast, for the emotion regulation executive network, there was no difference NSAC and LTAA with a current MDD Dx (Fig. 4; $F_{1,75} = 0.002$, $p = 0.96$, $es = 0.0\%$). Comparing LTAA with vs. without a current MDD Dx, those with a current MDD Dx had higher inhibitory control network RSS (Fig. 3; $F_{1,38} = 5.11$, $p = 0.03$, $es = 11.9\%$) and numerically (but not statistically) lower emotion regulation network RSS (Fig. 4.)

3.4. Appetitive drive RSS as related to a current MDD diagnosis

Comparing appetitive drive RSS in LTAA-MDDNR vs. NSAC showed lower RSS in LTAA-MDDNR vs. NSAC (Fig. 5; $F_{1,99} = 15.7$, $p < 0.001$, $es = 13.7\%$), with no cluster by group interaction (i.e., the difference between groups was comparable for the four appetitive drive clusters ($F_{3,97} = 1.81$, $p = 0.15$, $es = 5.3\%$)). Comparing appetitive drive RSS in LTAA-MDDC vs. NSAC showed no difference in RSS (Fig. 5; $F_{1,75} = 0.70$, $p = 0.40$, $es = 0.9\%$), with a comparable lack of effects across clusters ($F_{3,73} = 0.54$, $p = 0.65$, $es = 2.2\%$). Appetitive drive RSS was higher in MDDC than MDDNR (Fig. 5; $F_{1,38} = 9.03$, $p = 0.005$, $es = 19.2\%$), with this comparison being comparable across appetitive drive clusters ($F_{3,36} = 1.94$, $p = 0.14$, $es = 14.0\%$).

3.5. MDD symptom and alcohol onset results

Examination of the onset of MDD symptoms in LTAA subjects with a current and/or lifetime MDD diagnosis, revealed those with a current MDD had a significantly younger average age of onset for endorsed MDD symptoms than those with a lifetime but not current MDD diagnosis (19.5 vs. 27.2 yrs'; $p = 0.045$, $\eta^2 = 10.4\%$); see Table 1. This effect was still present when gender was included as a fixed factor ($p = 0.040$, $\eta^2 = 11.5\%$). There was no effect of gender ($p = 0.310$) and no interaction effect ($p = 0.634$) on MDD symptom onset age. No group differences were found between current and lifetime MDD LTAA subjects in age of first drink ($p = 0.336$), onset age of heavy drinking ($p = 0.645$), or age of ALC dependence onset ($p = 0.151$).

4. Discussion

In our prior work on LTAA, we focused on the central role of the externalizing diathesis in alcoholism and on whether the neurobiological disinhibitory underpinnings of externalizing illness changed with long-term abstinence, or whether the predisposition and disinhibitory engine was unchanged, but kept in check by higher cognitive functions and other adaptive changes. We have previously been able to elucidate some of these adaptive changes using rs-fMRI. Multi-year abstinent LTAA show an organization of resting state networks which, when compared to NSAC, manifests as lower signal exchange in appetitive drive networks and higher signal exchange in inhibitory control and emotion regulation networks

(Camchong et al., 2013a). We also found similar effects, although to a lesser degree, in short-term (~6–15 weeks abstinent) abstinent alcoholics (STAA) (Camchong, Stenger, & Fein, 2013b). We believe these cross-sectional findings reflect adaptive changes that support abstinence, both because of the observation of graded effects in short-term vs. long-term abstinence and because these networks play important roles in the changes needed for continued abstinence, where inhibiting behavior and reducing appetitive drive are central (Hare, Camerer, & Rangel, 2009; Medalla & Barbas, 2009; Naqvi & Bechara, 2010). The results are consistent with our prediction that LTAA with a current MDD diagnosis did not show reduced appetitive drive network RSS seen in other LTAA because they did not have the impulsive and compulsive “drive” towards alcohol consumption that other LTAA did, but rather their drive toward alcohol consumption was a coping mechanism associated with their depression.

Understanding the neurobiology of long-term abstinence is of the highest importance – the changes that take place in successful long-term abstinence should inform treatment. Treatment approaches to facilitate abstinence maintenance in alcoholics should aim to enhance RSS of the inhibitory executive control network and the emotion regulation executive control network and to attenuate RSS of the appetitive drive network. For example, we are working on EEG neurofeedback to modify resting state network synchrony (G. Fein & Cardenas, 2015). In that paper, we report promising preliminary findings using 64 channel resting EEG, showing that the coherency matrix contains Independent Components (ICs generated by Independent Components Analysis - ICA) that vary in conjunction with our rs-fMRI network synchrony measures (G. Fein & Cardenas, 2015). In other words, we find ICs that mimic the executive control rs-fMRI group differences, and other ICs that mimic the appetitive drive rs-fMRI group differences – with the appetitive drive group differences being opposite in direction to the executive control findings. The results of the current study may help us tailor approaches such as this to the heterogeneity present in the population of recovering alcoholics. For example, the most efficacious neurofeedback approach for alcoholics self-medicating for a MDD would be to train enhanced RSS of the inhibitory executive control network, but not train attenuation of RSS in the appetitive drive network. Additionally, neurofeedback to enhance RSS of the emotion regulation executive control network may facilitate efforts to address such individuals’ depressive problems. A major limitation of the current study is the relatively small number of LTAA with a current MDD, limiting the breadth of our knowledge of the LTAA current MDD subgroup. Another limitation is that the current study is cross-sectional and, although consistent with changes in network RSS in the various LTAA groups with long-term abstinence; proof of changes with continuing abstinence could only be demonstrated in longitudinal studies.

The results reported here have clinical significance because they bring focus on a previously ignored phenomenon indicating significant psychiatric morbidity in LTAA. We believe there is possibly a sizeable pool of individuals with MDD (and possibly with other mood and anxiety disorders) who are muddling along in life within the 12-step recovery community. Twelve-step recovery supports such individuals sufficiently for them to remain sober – and we are in no way disparaging the importance of this accomplishment. Yet we believe such individuals could be much more productive, happy, and have a generally greater quality of

life were their mood or anxiety disorder efficaciously treated. The results reported here are a first step toward identifying individuals who warrant developing targeted intervention and treatment approaches to accomplish this goal.

This work is also important because it focuses on heterogeneity within the LTAA population. It is clear that LTAA samples may differ in the proportion of individuals showing the pattern of current MDD. We have also found that LTAA samples may differ in other ways. For example, in California, we did not observe reduced subcortical volumes in LTAA (Goodro, Sameti, Patenaude, & Fein, 2012). More recently, we found lower volumes in LTAA vs. NSAC for the Accumbens, Hippocampus, Pallidum, Putamen and Thalamus in our Oahu samples (G Fein & Fein, 2013). We believe this difference in results is likely due to a combination of sample differences and imaging protocol improvements in Oahu vs. California. The Oahu sample did not differ in age from the California sample, but started drinking on average 1.5 years earlier ($p = 0.026$, effect size 3.1% of dependent variable variance). They also had much less education ($p \ll 0.0001$, $es = 13.9\%$), much higher body mass indices ($p \ll 0.0001$, $es = 10.1\%$), and a trend toward greater alcohol doses ($p = 0.078$, $es = 2.0\%$). Imaging studies on Oahu were carried out on a 3.0 T magnet vs. a 1.5 T magnet in California, with 5-year newer software and hardware in Oahu. Thus, LTAA in Oahu were not as healthy as those in California (much higher BMI) and were much less highly educated than those in California (possibly indicating less brain functional reserve capacity) – both of these factors may have limited their capacity for recovery from the brain morbidity of alcoholism (thus evidencing lower subcortical volumes than NSAC, even after multi-year abstinence). Additionally, greater alcohol use may have given them a greater alcohol brain morbidity to recover from. Finally, the improved imaging protocol in Oahu may have been more sensitive in measuring the effects of alcoholism on subcortical structures. We believe a major import of this result, and the results of the current study, is that one cannot generalize from one study of LTAA to the population of LTAA. LTAA cohorts may differ in alcoholism severity and in their ability to recover from such burden. It is only by the consistent decade long focus on this issue (and our laboratory moving from California to Hawaii) that we are able to make such observations. Our experience points out the importance to the research endeavor of multiple laboratories studying the clinical and neurobiological underpinnings of long-term abstinence.

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Fig. 1.

The networks involved in executive control that differ between long-term abstinent alcoholics (LTAA) and non-substance abusing controls (NSAC) are illustrated on the left. LTAA had higher resting state synchrony (RSS) than NSAC (1) between bilateral nucleus accumbens seeds (yellow) and left dorsolateral prefrontal cortex (DLPFC; red), involved with inhibitory executive control and (2) between subgenual anterior cingulate cortex seed (green) and right DLPFC (red), involved with executive control related to emotion regulation. Higher synchrony in LTAA compared to NSAC collapsed over the executive control networks is shown on the right.

Fig. 2.

The networks involved in appetitive drive that differ between long-term abstinent alcoholics (LTAA) and non-substance abusing controls (NSAC) are illustrated on the left. Lower resting state synchrony (RSS) was observed in LTAA compared to controls (1) subgenual anterior cingulate cortex (sgACC) seed with thalamus and caudate and (2) nucleus accumbens seeds with thalamus and caudate. Lower synchrony in LTAA compared to NSAC collapsed over the appetitive drive networks is shown on the right.

NAcc-Left DLPFC Resting State Synchrony

Fig. 3.

In the inhibitory control network, resting state synchrony comparisons between non-substance abusing controls (NSAC), long-term abstinent alcoholics (LTAA) with current major depressive disorder (MDD - current), and LTAA with no lifetime major depressive disorder or with major depressive disorder in remission (MDD - never and MDD - remission collapsed to form MDDNR) show that both subgroups of LTAA MDD show higher synchrony compared to NSAC, suggesting adaptive increases in inhibitory control help maintain abstinence.

sgACC-Right DLPFC Resting State Synchrony

Fig. 4.

In the emotion regulation network, resting state synchrony comparisons between non-substance abusing controls (NSAC), long-term abstinent alcoholics (LTAA) with current major depressive disorder (MDD - current), and LTAA with no lifetime major depressive disorder or with major depressive disorder in remission (MDD - never and MDD -remission collapsed to form MDDNR) show that LTAA with MDD - current do not show higher synchrony compared to controls, suggesting that LTAA MDD - current do not adapt their emotional regulation during long term abstinence.

Appetitive Drive Resting State Synchrony

Fig. 5.

In the appetitive drive networks, resting state synchrony comparisons between non-substance abusing controls (NSAC), long-term abstinent alcoholics (LTAA) with current major depressive disorder (MDD - current), and LTAA with no lifetime major depressive disorder or with major depressive disorder in remission (MDD - never and MDD - remission collapsed to form MDDNR) show that LTAA with MDD - current do not show reduced appetitive drive compared to controls.

Table 1

Demographics and clinical measures for long-term abstinent alcoholics (LTAA) with and without major depressive disorder (MDD) and non-substance abusing controls (NSAC).

	LTAA MDD						NSAC		Effect Size partial η^2	
	None			Lifetime in remission			Current		Ale vs. NSAC	MDD Diagnosis
	Φ (n=7)	σ (n=14)	Φ (n=8)	σ (n=3)	Φ (n=2)	σ (n=6)	Φ (n=34)	σ (n=35)		
Age (yrs)	44±4	50±5	52±6	36±1	51±7	49±8	49±8	50±7	0.2	1.3
Education (yrs)	12±1	13±2	14±1	14±1	13±8	14±3	16±3	16±3	20.2***	4.8
Alcohol FHD	0.43±0.35	0.28±0.28	0.36±0.22	0.22±0.38	0.27±0.18	0.2±0.30 (n=5) ^d	0.18±0.2 (n=33) ^d	0.13±0.19 (n=34) ^d	9.5**	2.2
Average Dose (drinks/mo)	290±94	211±180	122±85	248±154	413±531	361±257	7±7	10±9	46.6 ^d	11.5
Peak Dose (drinks/mo)	476±192	368±269	248±208	403±298	600±636	583±417	15±15	17±15	52.1 ^d	9.8
Age at first drink (yrs)	13±2	15±4	18±4	17±2	15±2	13±2	21±8 (n=32) ^b	14±6 (n=34) ^b	13.2***	15.6
Age met criteria for heavy drinking	16±2	23±8	25±10	19±1	26±3	16±2	N/A	N/A	N/A	2.4
Abstinence Duration in wks (range)	216±200 (87–550)	428±498 (84–1679)	457±381 (76–1080)	421±323 (183–789)	548±622 (109–988)	331±288 (88–874)	N/A	N/A	N/A	1
Age met Alcohol Dependence criteria	25±10	24±7	31±11	17±2	20±6	21±6	N/A	N/A	N/A	3.5
Average age of MDD symptom onset	33±9 (n=5) ^c	30±13 (n=9) ^c	33±14	19±4	12±1	22±9	27±12 (n=13) ^c	29±15 (n=8) ^c	0	20.9*
Lifetime mood disorders (N)	0	3	8	3	2	6	10	6	Odds ratio	Odds range
Current mood disorders (N)	0	1	0	0	2	6	3	1	4.0**	0.2, ∞, ∞ ^d
Lifetime anxiety disorders (N)	3	4	2	0	2	2	3	2	4.8*	0.1, 0, ∞ ^d
Current anxiety disorders (N)	1	1	1	0	1	1	1	0	6.3***	0.5, 0.2, 1
Lifetime externalizing disorders (N)	7	11	7	3	2	6	6	20	10.0*	0.1, 0.1, 0.3
Current externalizing disorders (N)	0	1	1	1	1	1	0	2	14.3***	6, 10, ∞

Statistical Significance:

* p < 0.05;

** p < 0.01;

*** p < 0.001.

^d n is reduced - we could not ascertain the histories for adopted participants.

statistical comparisons are invalid since this variable is related to the inclusion criteria.

A

n is reduced for subjects that have no MDD symptoms.

c

n is reduced because some subjects never drank.

q

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