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P3b Amplitude is not reduced in abstinent alcoholics with a current MDD

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Abstract

Background and Aims: In two studies of long-term abstinent alcoholics (LTAAAs), we found that about 17% had a current major depressive disorder (MDD). We tested the hypothesis that LTAAAs with a current MDD diagnosis do not exhibit the reduced P3b event-related potential amplitude endophenotype for alcoholism. This is consistent with the majority of LTAAAs with a current MDD having developed alcohol dependence via self-medication of their MDD rather than their alcohol dependence arising from the alcoholism endophenotype.

We revisited the P3b data from the two LTAAAs studies, comparing LTAAAs with a current MDD vs. LTAAAs without a current MDD to each other and to non-substance abusing controls (NSACs). In northern California, 48 LTAAAs and 48 non-substance abusing controls were studied, while in Honolulu, 105 LTAAAs and 77 NSACs were studied. A total of 26 LTAAAs had a current MDD (10 in California and 16 in Honolulu). The difference in P3b amplitude and latency (measured in targets-standards) in a 3-condition visual oddball paradigm was compared to MDD diagnoses gathered using the computerized Diagnostic Interview Schedule. Across both study sites, LTAAAs without a current MDD (either with no lifetime MDD or a lifetime, but not current MDD) had lower P3b amplitudes than NSACs. In contrast, P3b amplitudes in LTAAAs with a current MDD did not differ from controls. We conclude that alcohol dependence in LTAAAs with a current MDD did not derive from the alcoholism endophenotype. This group may not exhibit the externalizing diathesis characterized by impulsive, disinhibited behavior and may have developed alcohol dependence via excessive drinking in an attempt to self-medicate their MDD. These results have major implications for targeted treatments of alcoholism and comorbid MDD.

Keywords

alcohol dependence; self-medication; P3b; major depressive disorder

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Introduction

Major depression is highly prevalent in the general population and is one of the leading causes of disability in the United States (The World Health Organization. *The global burden of disease: 2004 update*), affecting about 6.7% of the U.S. population aged 18 or older. Alcohol-use disorders affect similarly large proportions of the U.S. population, with major costs to society in family and work life as well as health care. The comorbidity of AUDs and major depression disorder (MDD) has been well documented in studies of inpatient populations in treatment for alcohol-use disorder and/or MDD (Helzer & Pryzbeck, 1988; Regier et al., 1990), as well as in large scale epidemiologic surveys on alcohol-use disorder and related conditions, which report comorbid rates of MDD as high as 20.5% (Grant & Dawson, 2006; Grant et al., 2009; Grant, Hasin, Chou, Stinson, & Dawson, 2004; Grant, Stinson, Dawson, Chou, Dufour, et al., 2004; Grant, Stinson, Dawson, Chou, Ruan, et al., 2004; Greenfield et al., 1998; Hasin, Stinson, Ogburn, & Grant, 2007) of the AUD population. Clinically, either disorder can influence the other disorder in negative ways.

Two previous studies in our lab further highlight this issue. In a cross-sectional study on the island of Oahu, we recently showed that about one-third of middle-aged long-term (>1.5 years) abstinent alcoholics (LTAAAs, $n = 110$) had a lifetime major depressive disorder diagnosis, about double the rate of 17% in age- and gender-comparable non-substance abusing controls (NSACs, $n = 82$) (Fein, 2013). In 2007, we had found a comparable difference in analogous groups of 52 LTAAAs and 48 NSACs in northern California (Di Sclafani, Finn, & Fein, 2007). Although current diagnosis rates are lower than lifetime rates (i.e., current diagnoses are a subset of lifetime diagnoses), the differences in the percentage of individuals with current MDD between alcoholic and control groups were actually larger. On Oahu, compared to 2.4% of controls, 14.5% of LTAAAs had a current MDD diagnosis. In northern California, current MDD was present in 4.2% of NSACs vs. 19.2% of LTAAAs.

We propose that the majority of LTAAAs with a **current** MDD diagnosis had a primary depression that they self-medicated with alcohol (often with drugs also). The combined burden of a MDD and alcohol dependence (sometimes also with drug dependence) may have driven 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, many of them have not been particularly successful in dealing with their MDD. By group inclusion criteria, all meet criteria for a current MDD. If their efforts to deal with their MDD had been successful, one would expect the disorder to be in remission. Indeed, previous investigations of alcoholics have indicated that with successful treatment of the AUD, MDD symptoms often resolve (Brown et al., 1995; Penick, Powell, Liskow, Jackson, & Nickel, 1988). However, other studies have suggested that comorbid depression does not affect alcohol treatment outcomes and in some cases may actually be associated with a better recovery rate from AUDs (Burns, Teesson, & O'Neill, 2005; Greenfield et al., 1998; Hasin & Grant, 2002; Hesselbrock, Meyer, & Keener, 1985; Loosen, Dew, & Prange, 1990; Rounsaville, Dolinsky, Babor, & Meyer, 1987; Schuckit, 1983). The question of disease primacy can have important implications on these findings. If comorbid MDD is secondary to the AUD (i.e., the toxic effects of ethanol lead to depressive symptoms, or a secondary effect of alcohol – loss of job – leads to depression), then extended abstinence from alcohol

should also help alleviate the MDD. However, if the MDD is primary and the AUD is a reactionary consequence (i.e., self-medication), then treatment of the AUD may be easier, but the MDD may persist, even with extended abstinence from alcohol.

We recently examined rs-fMRI data for LTAAAs and NSACs from Hawaii and showed that LTAAAs with a current MDD diagnosis did not show the reduced appetitive drive network resting-state synchrony (RSS) seen in LTAAAs without a current depression, suggesting that alcohol dependence in LTAAAs with a current MDD did not derive from an impulsive and compulsive “drive” toward alcohol consumption, but rather developed as a coping mechanism associated with their depression (Fein, Camchong, Cardenas, & Stenger, 2017). In the current manuscript, we are testing the hypothesis that, in comparison to LTAAAs without a current MDD diagnosis, individuals with a current MDD diagnosis are less likely to exhibit the reduced P3b event-related potential (ERP) amplitude endophenotype for alcoholism. In other words, we hypothesize that LTAAAs with a current MDD did not have a genetic basis for their alcohol dependence to the degree that LTAAAs without a current MDD did. The low amplitude of the P3b, the P300 ERP component elicited during oddball tasks in response to the target stimulus maximal over the midline posterior brain, is a well-documented and robust finding (Begleiter & Porjesz, 1999; Begleiter, Porjesz, Bihari, & Kissin, 1984; Fein & Chang, 2006; Iacono, Malone, & McGue, 2003). It has been proposed as an endophenotypic marker for alcoholism and externalizing disorder vulnerability (Bauer & Hesselbrock, 1999; Begleiter et al., 1984; Cohen, Porjesz, Begleiter, & Wang, 1997; Hill et al., 1998; Pfefferbaum, Ford, White, & Mathalon, 1991). Lower P3b amplitude is present for both auditory and visual target detection tasks, with the effect being more prominent in visual paradigms. A review of P300 in substance-use disorders by Euser and colleagues (2012) found that the lower P300 amplitude associated with SUDs is of medium-effect size (Cohen’s $d = 0.51$).

P300 oddball (primarily auditory) paradigms have also been used to study MDD. The results have been nowhere near as robust or consistent as the alcoholism results. Some studies report lower P3b amplitude in subjects with MDD vs. controls (Anderer, Saletu, Semlitsch, & Pascual-Marqui, 2002; Blackwood et al., 1987; Muir, St Clair, & Blackwood, 1991; Roschke & Wagner, 2003; Wagner, 2003), but a number of studies report no difference (Bruder et al., 1998; Himani, Tandon, & Bhatia, 1999; Vandoolaeghe, van Hunsel, Nuyten, & Maes, 1998). To date, a few investigations have looked at visual P3b in MDD subjects, also with varied results (Diner, Holcomb, & Dykman, 1985; but see Bange & Bathien, 1998). Taking these findings into account, we expect that a current MDD may lead to little effect on P3b amplitude. If there is an effect, it would likely be in the opposite direction (lower vs. same as controls) as our proposed hypothesis, that LTAAAs with current MDD will not demonstrate the externalizing endophenotypic marker of lower P3b amplitude when compared to controls.

In this manuscript, we are revisiting P3b ERP data previously published, in which we demonstrate reduced P3b amplitude compared to NSACs in middle-aged LTAAAs – both in the San Francisco Bay Area (Di Scialfani et al., 2007) and on the island of Oahu (Fein, 2013). Our hypothesis in the current study is that if we divide the LTAA samples into subgroups based on whether or not individuals met criteria for a current MDD diagnosis, the

subgroup with a current MDD diagnosis would not exhibit reduced P3b, consistent with the notion that their alcohol dependence did not result from the alcoholism endophenotype.

Material and methods

Participants

Four samples of subjects from two prior projects were analyzed in the current study. The first two samples had been recruited and studied in the San Francisco Bay Area, and consisted of forty-eight 35–60-year-old LTAAAs with a minimum of 6 months abstinence, averaging 6.3 ± 5.8 years abstinence, and 48 age- and gender-comparable NSACs. The LTAA experimental groups excluded individuals with comorbid lifetime drug abuse or dependence (other than nicotine or caffeine). The other two samples, recruited and studied in the greater Honolulu area on the island of Oahu, consisted of comparably aged LTAAAs ($n = 105$, with a minimum abstinence duration of 1.5 years and a mean abstinence duration of 7.6 years), and NSACs ($n = 77$). The Hawaii LTAA samples included individuals with comorbid lifetime drug abuse/dependence. The subjects cited above exclude a total of 12 subjects across both sites who did not have EEG/ERP recordings and two subjects that did not have enough trials after EEG pre-processing to provide reliable waveform data.

All individuals in both studies were recruited through postings at AA meetings, community and treatment centers, and participant referrals. LTAAAs in northern California ($n = 48$, 23 women and 25 men) met DSM-IV criteria for lifetime alcohol dependence, were between 34.4 to 59.8 years of age (mean = 45.7 years), and were abstinent from 25–1110 weeks (mean = 349 ± 307 weeks). LTAAAs in Oahu ($n = 105$, 50 women and 55 men) also met DSM-IV criteria for lifetime alcohol dependence, were between 35.0 to 60.8 years of age (mean = 48.7 years), and were abstinent from 75.6–1678.6 weeks (mean = 396 ± 337 weeks). NSACs ($n = 48$ in California, 23 women and 25 men; $n = 77$ on Oahu, 39 women and 38 men) were between 34.4 and 60.9 years of age (mean = 47.4 years). NSACs had a lifetime drinking average of fewer 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 a 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, stroke, or hypertension that required medical intervention, 3) history of significant neurological disease, 4) laboratory evidence of hepatic disease, 5) clinical evidence of Wernicke-Korsakoff syndrome, 6) reported evidence of benzodiazepine use, and 7) lifetime or current diagnosis of schizophrenia or schizophreniform disorder as determined by the c-DIS (computerized-Diagnostic Interview Schedule, see below). As noted above, in California, LTAAAs were excluded if they had a lifetime drug abuse or dependence diagnosis, while about half of LTAAAs on Oahu who were selected had comorbid drug dependence. After a complete description of the study to the subjects, written informed consent was obtained.

Alcohol and Substance Use, Abuse, and Dependence

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). These procedures yielded alcohol average dose, alcohol peak dose, and abstinence duration. In California, individuals with a lifetime drug abuse or dependence diagnosis (other than nicotine or caffeine) were excluded. In Hawaii, lifetime alcohol, cocaine, methamphetamine, THC, and nicotine use were determined, as were diagnoses of abuse or dependence.

Family History of Problem Drinking

The Family Drinking Questionnaire (Mann, Sobell, Sobell, & Pavan, 1985) was administered with regard to drinking. Participants rated family members as abstainers, users with no problem, or problem users. The Family History Density of Alcohol Problems was the proportion of first-degree relatives identified as problem drinkers.

Psychiatric Diagnoses

The c-DIS (Bucholz et al., 1991; Erdman et al., 1992; Levitan, Blouin, Navarro, & Hill, 1991; Robins, Cottler, Bucholz, & Compton, 1995) 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 many lifetime and current diagnoses in the mood, anxiety, and externalizing domains. For the purpose of the current paper, only current diagnoses of MDD were used. MDD was by far the major internalizing psychiatric diagnosis present in these samples (Fein, 2013). Additionally, subjects studied at the Oahu test site reported the age of onset for endorsed symptoms of MDD and externalizing domain symptom counts.

EEG Measures

Experimental Paradigm—All stimuli were presented on a computer monitor using the E-prime software system (Schneider, Eschman, & Zuccolotto, 2002). Stimuli were presented on a black screen for 200 ms, followed by a delay varying between 1000 and 1100 ms before the next stimulus. Three different types of visual stimuli were presented: 1) standard stimuli: a small hollow white square; 2) target stimuli: a small white X; and 3) novel rare non-target stimuli: different shapes of various colors. Participants were instructed to press a response box button only when they saw target stimuli. Stimuli were presented in a predetermined order, with standard stimuli appearing 210 times, target stimuli appearing 35 times and rare non-target stimuli appearing 35 times over approximately 6.5 minutes. Each participant was shown an example of the target stimulus before the task began.

EEG Acquisition and Analysis

EEG acquisition methods have been detailed in previous reports (Andrew & Fein, 2010; Fein & Chang, 2006; Gilmore & Fein, 2013); they are briefly outlined here. EEG was acquired using NuAmps and SynAmps2 systems and Scan acquisition software (Compumedics, 2003). Electrode impedances were maintained below 10 k Ω . Vertical

electro-oculogram (EOG) was recorded from a bipolar electrode site pair placed above and below the left eye for later reduction of ocular artifact. The sampling rate was 250 samples/sec for EEG and EOG channels.

EEG recordings were processed offline using the Edit program in Scan 4.5 (Compumedics, 2003). Artifacts from eye movements were removed using the ARTCOR procedure, then the data were bandpass-filtered between 0.5 Hz and 15 Hz using a zero phase lag filter with a 48 dB/octave roll-off. Epochs of 850 ms were extracted for all standard, target, and rare non-target trials with a correct behavioral response. Epochs included 100 ms pre-stimulus to 750 ms post-stimulus. Trials were baseline corrected using the 100-ms immediate pre-stimulus interval. Any trials containing out of range voltages ($\pm 75 \mu\text{V}$) were rejected as artifacts and excluded from further processing. P3b amplitude was measured for each subject on the difference waveform by subtracting the average ERP response to the standard stimulus from the average ERP response to target stimuli (having the correct behavioral response). Difference waves were chosen for analysis because the P3b signal is the largest and most easily extracted from difference waves, while components that are present in response to both target and standard stimuli are largely removed. P3b amplitude was measured as the peak amplitude in the 250–550-ms post-stimulus interval of these difference waves, using the PEAK DETECT procedure at electrode Pz. Although the P3b may not be maximal at Pz for all subjects, our examination of subject topographical maps did not suggest a group-related shift in P3b topography, so we chose to simplify our analyses by measuring at a single electrode. Because our hypothesis was focused on P3b, other components elicited by our oddball paradigm were not analyzed.

Statistical analysis

P3b data was analyzed using the General Linear Model procedure in SPSS (SPSS Inc., 2009). Two separate ANOVAs were conducted investigating P3b amplitude and latency. Each ANOVA had MDD diagnosis (LTAAAs with no diagnosis or in remission vs. LTAAAs with a current diagnosis vs. controls), study site (California vs. Oahu), and gender as fixed effects. *Post hoc* analyses for multiple comparisons examined differences between the MDD diagnosis groups.

Results

Demographic results

Table 1 presents demographic and alcohol-use data for both the California and Oahu studies; the data for each study are divided by NSACs and the three subgroups of LTAAAs (no Lifetime MDD, Lifetime MDD in Remission, and Current MDD). Comparisons in the table compare NSAC vs. the combined LTAA samples, and compare the three LTAA subsamples. The table shows that within each study, NSACs and LTAAAs were comparable in age, LTAAAs had less education than NSACs in Hawaii but not California, and NSACs had a lower family history density of alcohol problems than LTAAAs in both California and Hawaii. The table also shows the dramatic differences between NSACs and LTAAAs in alcohol-use measures consistent with LTAAAs being chronic alcoholics. The LTAA subgroups did not differ on any

alcohol measure, showing that any differences we find below in P3b amplitude and latency are not a function of differences in alcohol intake.

Data on nicotine use were acquired only for the Hawaii participants. In addition, Hawaii comorbidity for other substance use was not exclusionary for the Hawaii studies. Nicotine use and other substance dependences were examined for their effect on P3b amplitude and latency. There were no significant effects of other substance dependence on P3b amplitude ($p = 0.86$) or latency ($p = 0.94$), and no significant effects of nicotine dependence on either measure (amplitude: $p = 0.22$; latency: $p = 0.41$).

P3b results

Fig. 1 shows the target-standard time series for the four groups: NSACs, LTAAAs with current MDD, LTAAAs who have never had a MDD, and LTAAAs with a lifetime but no current MDD (remission). The time series are shown for 9 electrodes, and the California (black) and Hawaii (dotted) traces are superimposed. Because these are difference waves, the P3b component is magnified, and components earlier than the P300 (such as N1 and P2) are largely canceled out. Fig. 1 shows almost no difference between the two LTAA groups without a MDD, and t tests found no difference in either P3b amplitude ($p = 0.98$) or latency ($p = 0.45$). For all further statistical analyses, the two LTAA groups without MDD were collapsed into a single group. Fig. 2 shows maps of the P3b target-standard response for LTAAAs with a current MDD diagnosis, LTAAAs without a current MDD, and NSAC subjects, separately for each testing site. **P3b Amplitude:** Tests of between-subject effects revealed a significant difference in P3b amplitude between groups ($F_{(2,266)} = 12.4$; $p < 0.0001$, $\eta^2 = 8.5\%$), with no difference between sites (Oahu vs. California) ($F_{(1,266)} = 0.05$; $p = .82$, $\eta^2 = 0.0\%$), with no sex differences ($F_{(1,266)} = 0.48$; $p = .49$, $\eta^2 = 0.2\%$), and no significant interaction effects (all p 's > 0.42). *Post hoc* tests showed that LTAAAs without a current MDD diagnosis had lower P3b amplitude than both LTAAAs with a current MDD diagnosis ($p = .001$) and NSACs ($p < 0.000$), as shown by the bar charts in Fig. 3. NSACs and LTAAAs with a current MDD had comparable P3b amplitudes ($p = 0.56$). **P3b Latency:** There was no between-subjects MDD diagnosis effect for P3b target-standard latency, although *post hoc* tests suggested that LTAAAs without a current MDD diagnosis had longer P3b latencies than controls ($p = 0.024$). These results are illustrated in Fig. 4.

Anti-depressant medications

Of the 55 subjects from Hawaii who were diagnosed with a lifetime MDD, current anti-depressant medication information was available for 50 of them. When the use of current anti-depressant medication was added as a covariate in the linear model, the between-subject effect of MDD diagnosis was still significant ($p = 0.044$) for P3b amplitude measured from the target-standard waveforms.

MDD symptom and alcohol-onset results

Examination of the onset of MDD symptoms in LTAA subjects (Hawaii only) showed that those with a current MDD had a significantly younger average age of onset (mean = 19.5 years) for endorsed MDD symptoms than those with a lifetime but not current MDD diagnosis (mean = 27.2 years) and those without a lifetime MDD diagnosis (mean = 26.6

years) ($p = 0.023$, $\eta^2 = 6.1\%$). This effect was unchanged when sex was included as a fixed factor ($p = 0.022$, $\eta^2 = 6.5\%$). There was no effect of gender ($p = 0.310$) and no gender interaction effect ($p = 0.634$). 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 alcohol dependence onset ($p = .151$). There was a trend for AUD onset to precede MDD onset by a greater number of years in lifetime (but not current) MDD or never-MDD LTAA subjects compared to current MDD LTAA subjects ($p = 0.09$), and there was no effect of gender ($p = 0.502$) and no gender interaction effect ($p = 0.914$).

MDD symptoms and externalizing symptoms

If LTAA subjects with a current MDD diagnosis developed alcohol dependence via excessive drinking in an attempt to self-medicate their MDD, instead of as a result of a vulnerability to externalizing disorders, one might expect them to exhibit fewer externalizing symptoms than LTAA subjects without a current MDD. Examination of the number of lifetime and current externalizing symptoms in LTAA subjects (Hawaii only) showed no difference in the number of lifetime symptoms ($p = 0.67$) and a trend to a greater number of current externalizing symptoms (10 ± 9 vs. 7 ± 7 , $p = 0.09$) in LTAA subjects with a current MDD diagnosis.

Correlation Results

Alcohol-use variables, family history, MDD severity, and P3b measures were compared in a bivariate correlation (uncorrected for multiple comparisons) to examine any underlying relationships, within the alcoholics only. Most notably, longer abstinence duration was associated with longer P3b target-standard latency ($r = .204$, $p = 0.011$). Higher lifetime MDD symptom counts were associated with a higher family density of problem drinkers ($r = .180$, $p = .029$). In the Hawaii subjects only (current MDD symptom counts were not collected in California), more current MDD symptoms were associated with a higher lifetime alcohol dose ($r = .251$, $p = 0.010$) and a higher peak dose ($r = .323$, $p = 0.001$).

Discussion

The main findings of this study are: 1) there were lower target-standard P3b amplitudes in non-current MDD alcoholics when compared to LTAA subjects with a current MDD and controls; 2) there was an absence of lower target-standard P3b amplitudes in alcoholics with current MDD compared to controls; 3) within Hawaii subjects (the only site for which such data are available), those LTAA subjects with current MDD reported an earlier average age of onset for MDD symptoms than those without a current MDD diagnosis; and 4) within Hawaii subjects (the only site for which such data are available), there was evidence for a difference in the number of externalizing symptoms between LTAA groups. The findings of this study, that LTAA subjects with a **current** MDD diagnosis do not manifest lower P3b amplitudes compared to NSACs, as do those LTAA subjects without a current depression, support the hypothesis that current MDD LTAA subjects do not represent the externalizing/addiction endophenotype and its association with an externalizing diathesis characterized by impulsive, disinhibited behavior. Additionally, as a group, LTAA subjects with a current MDD diagnosis had an earlier age of onset of MDD symptoms. There was also a trend for AUD onset to precede MDD symptom onset

by a greater number of years in subjects with a history of MDD but without a current MDD. Although statistics revealed no sex differences or interaction effects regarding MDD onset, as Table 1 shows, the pattern of MDD symptom onset preceding AUD onset is clearest in women. Taken together, these results, obtained in a sizeable subset of subjects, support the hypothesis that LTAAAs with a current MDD diagnosis developed alcohol dependence via excessive drinking in an attempt to self-medicate their MDD. Proof of this hypothesis would require prospective longitudinal studies following MDD individuals through the initiation of drinking and development of alcohol dependence, and these results suggest that such studies are warranted.

In our prior work on LTAAAs, 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 was kept hidden by higher cognitive functions and other adaptive changes. We have been able to elucidate some of these adaptive changes using resting state functional connectivity magnetic resonance imaging (rs-fMRI). Multi-year abstinent LTAAAs show an organization of resting state networks which, when compared to NSACs, manifests as lower signal exchange in appetitive drive networks and higher signal exchange in inhibitory control and emotion regulation networks (J. Camchong, A. Stenger, & G. Fein, 2013). We also found similar effects, although to a lesser degree, in short-term (~6–15 weeks abstinent) abstinent alcoholics (STAA) (J. Camchong, V. A. Stenger, & G. Fein, 2013). 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). Regarding adaptive rs-fMRI resting state synchrony (RSS) changes, we recently showed that LTAAAs with a current MDD diagnosis do not show reduced appetitive drive network RSS seen in other LTAAAs, suggesting that they did not have the impulsive and compulsive “drive” toward alcohol consumption that other LTAAAs did. The current results augment the earlier study (on a subset of the Hawaii sample presented here) with additional data showing that LTAAAs with a current MDD diagnosis do not show strong evidence that the genetically determined vulnerability to an externalizing diathesis is part of the engine behind the development of their alcohol dependence.

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. For example, we are working on EEG neurofeedback to modify resting state network synchrony. We have promising preliminary findings using 64-channel resting EEG, showing that the coherency matrix contains independent components (ICs) (ICs generated by Independent Components Analysis – ICA) that vary in conjunction with our rs-fMRI network synchrony measures. 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. We see this effort moving toward development of an EEG RSS neurofeedback treatment approach to facilitate abstinence maintenance in alcoholics, enhancing RSS of the

executive control network to facilitate inhibitory control and attenuating RSS of the appetitive drive network to decrease the compulsive search for reward. 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 executive control network, but not train attenuation of RSS in the appetitive drive network.

A limitation of the current study is the relatively small number of LTAAAs with a current MDD (26 subjects across the two study sites). This limitation is largely overcome by the replication of results across the two sites (there were no group-by-site [California vs. Hawaii] interaction effects), so we are convinced of the validity and replicability of the P3b amplitude result. However, the small sample size limits the breadth of our knowledge of the LTAA current MDD subgroup. A second limitation of the analysis was measurement of P3b amplitude and latency at a single electrode. The topographical maps in Fig. 2 suggest that the P3b was maximal over parietal scalp regions for all groups, and thus a single electrode measurement is appropriate. However, a source analysis that utilizes multichannel data would help differentiate whether the observed difference in amplitude across groups reflects a reduction in neural source strength or a different configuration of neural sources.

The results reported here have clinical significance because they bring focus to a previously ignored phenomenon indicating significant psychiatric morbidity. We believe there is a sizeable pool of individuals with MDD (and possibly with other mood and anxiety disorders) 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 if their mood or anxiety disorder were to be efficaciously treated. The results reported here are a first step toward developing targeted intervention and treatment approaches to accomplish this goal.

This work is also important because it focuses on heterophenotypy 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, reviewed in our recent paper on rs-fMRI vs. current MDD diagnoses (Fein et al., 2017). For example, Figs. 1 and 2 show that P3b latency is longer in all Hawaii groups compared to all California groups. LTAAAs 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 be related to longer P3b latencies. We believe a major import of these phenomena is that one cannot generalize from one study of LTAAAs to the population of LTAAAs. LTAA cohorts may differ in alcoholism severity and in their ability to recover from such a burden. 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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Abbreviations

AUD	alcohol-use disorders
MDD	major depressive disorder
LTAAs	long-term abstinent alcoholics
NSACs	non-substance abusing controls

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Highlights

- We have recently shown that LTAAAs with a current MDD diagnosis do not have the same externalizing diathesis driving their alcohol dependence as do LTAAAs without a current MDD diagnosis.
- In this paper, we examine P300 amplitudes in data from the study mentioned above, and in LTAAAs and control samples from northern California.
- Consistent with our earlier paper examining rs-fMRI functional connectivity, P300 is not reduced in LTAAAs with a current MDD diagnosis, showing they likely do not have the genetic predisposition to externalizing disorders.
- Different brain activity patterns and treatment needs are suggested in alcoholics with a current MDD vs. alcoholics without a current MDD.

Fig. 1.

Traces of the group-averaged target-standard waveforms are shown for NSACs (non-substance abusing controls) and LTAAAs (long-term abstinent alcoholics) subdivided into MDD (major depressive disorder) groups (current, never, and in remission). Waveforms are shown for 9 electrode sites, and the average waveforms for the two testing sites are superimposed. Asterisks identify the P3b component at electrode Pz.

Fig. 2.

This figure shows maps of the P3b response for LTAA with a current MDD diagnosis, LTAA without a current MDD, and control subjects, separately for each testing site. The figure illustrates the similarity of the basic result across testing sites – that P3b is reduced in LTAA without a current MDD diagnosis, but it is not reduced in LTAA with a current MDD diagnosis. The figure also shows a later latency of P3b in the Hawaii vs. California samples.

Fig. 3.

P3b amplitudes are shown for NSACs (non-substance abusing controls) and LTAAAs (long-term abstinent alcoholics) subdivided into MDD (major depressive disorder) groups (current, never, and in remission) distinguished by study site. The amplitude effects are essentially equivalent across study sites. Because no differences were found between MDD-never and MDD-remission, these groups were collapsed for comparison to NSACs and MDDcurrent. *Post hoc* tests suggested that only LTAAAs without a current MDD diagnosis showed P3b reduction associated with the alcoholism endophenotype.

Fig. 4.

P3b latencies are shown for NSACs (non-substance abusing controls) and LTAA (long-term abstinent alcoholics) subdivided into MDD (major depressive disorder) groups (current, never, and in remission), distinguished by study site. The latency group effects are similar across study sites, although P3b latencies were longer in all Hawaii groups. Because no differences were found between MDD-never and MDD-remission, these groups were collapsed for comparison to NSACs and MDD-current. *Post hoc* tests suggested that LTAA without a current MDD diagnosis had longer P3b latencies than controls ($p = 0.024$). LTAA with a current MDD diagnosis did not differ in P3b latency from either NSACs or LTAA without a current MDD diagnosis.

Table 1

Demographics and Alcohol-Use Variables

Hawaii											
	LTAA – MDD Dx						NSAC			Effect Size (partial η^2)	
	None		In Remission		Current		$\bar{g}$ (N=39)	σ^2 (N=38)	Alc vs. NSAC	MDD Diagnosis	
	$\bar{g}$ (N=28)	σ^2 (N=36)	$\bar{g}$ (N=15)	σ^2 (N=10)	$\bar{g}$ (N=7)	σ^2 (N=9)					
Age (yrs)	46±6	49±6	51±7	45±9	53±6	49±7	49±8	48±7	0	3.6	
Education (yrs)	13±2	13±2	14±2	14±3	14±4	14±2	16±3	16±3	18.4***	2.3	
Alcohol FHD	(N=25) .43±.32	(N=35) .24±.25	.42±.31	.29±.35	.41±.31	(N=8) .35±.36	(N=38) .21±.23	(N=37) .13±.18	9.3***	1.0	
Alcohol use											
Average Dose (drinks/mo)	193±139	197±143	148±88	261±166	258±270	259±223	8±8	10±9	39.8 ^A	2.2	
Peak Dose (drinks/mo)	326±219	348±251	262±165	466±283	564±595	429±356	17±16	16±15	38.8 ^A	3.6	
Abstinence Duration (weeks)	368±306	338±369	460±356	504±338	579±544	279±252	N/A	N/A	N/A	1.9	
Age first drink ^b	13±4	14±5	16±4	14±4	14±3	14±3	(N=37) 21±9	(N=36) 18±6	18.9***	1.4	
Age first heavy use	18±4	20±7	22±9	18±3	21±8	20±6	N/A	N/A	N/A	1.3	
Avg Age MDD Sx onset ^c	(N=23) 27±12	(N=23) 27±11	(N=14) 26±13	28±14	16±6	(N=8) 22±9	(N=14) 30±12	(N=9) 30±15	1.5	6.6 ⁰⁷	
Avg Alc Dep onset	20±8	21±7	27±11	20±4	18±3	22±6	N/A	N/A	N/A	3.5	

California											
	LTAA - MDD Dx						NSAC			Effect Size (partial η^2)	
	None		In Remission		Current		$\bar{g}$ (N=23)	σ^2 (N=25)	Alc vs. NSAC	MDD Diagnosis	
	$\bar{g}$ (N=10)	σ^2 (N=11)	$\bar{g}$ (N=7)	σ^2 (N=10)	$\bar{g}$ (N=6)	σ^2 (N=4)					
Age(y)	50±7	46±6	47±6	48±7	48±7	39±8	48±7	44±6.2	0.8	5.8	
Education (yrs)	16±2	16±2	14±3	15±2	16±2	16±2	16±2	16±2.2	2.5	9.6	
Alcohol FHD	.40±.34	.43±.19	0.5±0.3	0.3±0.2	.44±.19	.65±.41	.17±0.2	.12±.18	26.8***	4.1	
Alcohol use											
Average Dose (drinks/mo)	160±106	171±138	115±46	190±133	102±40	108±74	7±8	6±8	48.2 ^A	4.8	
Peak Dose (drinks/mo)	356±282	322±207	204±51	368±188	203±113	204±136	17±22	14±14	50.8 ^A	7.1	

California										
	LTAA - MDD Dx						NSAC		Effect Size (partial η^2)	
	None		In Remission		Current					
	♀ (N=10)	♂ (N=11)	♀ (N=7)	♂ (N=10)	♀ (N=6)	♂ (N=4)	♀ (N=23)	♂ (N=25)	Alc vs. NSAC	MDD Diagnosis
Abstinence Duration (weeks)	360±498	399±333	270±212	328±369	383±306	223±268	N/A	N/A	N/A	2.5
Age first drink ^b	16±3	15±4	17±3	15±3	15±3	15±2	20±5	(N=23) 19±5	21.7***	2.8
Age first heavy use	24±5	20±3	26±7	22±3	24±9	27±8	N/A	N/A	N/A	5

Statistical Significance:

* $p < .05$;

** $p < .01$;

*** $p < .001$

^a n is reduced – we could not ascertain the histories for adopted participants

^b n is reduced because some subjects never drank

^c n is reduced for subjects that have no MDD symptoms

Statistical Significance:

* $p < .05$;

** $p < .01$;

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^a n is reduced • we could not ascertain the histories for adopted participants

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