Frontal Brain N-Acetylaspartate at Treatment Entry is Related to Future World Health Organization Risk Drinking Levels in Individuals With Alcohol Use Disorder

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ABSTRACT. Objective: The purpose of this study was to assess the viability of regional brain metabolite levels of individuals with alcohol use disorder (AUD) at treatment entry as a biomarker of posttreatment levels of alcohol use, categorized according to the World Health Organization risk drinking levels (WHO-RDL). **Method:** Eighty-five individuals initiating treatment for AUD (16 ± 13 days after last alcohol consumption) and 45 light/nondrinking controls completed a 1.5T proton multislice magnetic resonance spectroscopic imaging study. N-acetylaspartate (NAA), a marker of neuronal viability, and other metabolites were quantitated for cortical gray matter, white matter, and select subcortical regions. Individuals with AUD were classified according to their posttreatment alcohol consumption as abstainers (n = 42), low-risk (n = 20), or higher risk (n = 23) participants based on the WHO-RDL taxonomy. **Results:** Within frontal gray matter, higher risk participants exhibited significantly lower NAA levels than light/nondrinking controls and abstainers but did not differ from low-risk participants. Higher risk participants had significantly lower NAA concentration in frontal white matter than all groups who did not significantly differ from one another. Higher risk participants showed significantly lower parietal white matter NAA than light/nondrinking controls and abstainers; low-risk and higher risk participants did not differ from one another. Across higher risk and low risk, lower frontal gray matter and white matter NAA were related to shorter periods of abstinence before first posttreatment alcohol consumption and longer posttreatment duration of alcohol resumption. There were no significant group differences in myo-inositol or choline- or creatine-containing compound concentrations. **Conclusions:** Frontal and parietal lobar NAA concentrations, near treatment entry, are associated with WHO-RDL categorized posttreatment alcohol consumption levels and may serve as predictive biomarkers of clinical outcomes following treatment for AUD. (*J. Stud. Alcohol Drugs, 86,* 416–423, 2025)

INDIVIDUALS WITH alcohol use disorder (AUD) often experience a chronic cycle of resumption and remission, which is associated with considerable suffering and socioeconomic costs (Collins, 2016; Schuckit, 2022). Historically, complete abstinence from alcohol has been considered the primary "successful" outcome following treatment for AUD, given the associated improvements in health, cognition, and functioning (Sliedrecht et al., 2022; Witkiewitz et al., 2020). Harm-reduction interventions, however, are increasingly implemented treatment approaches, as accumulating evidence suggests that significant decreases in alcohol consumption, not solely abstinence, are associated with improved biopsychosocial functioning and may be more attainable for some (Knox et al., 2019; Witkiewitz et al., 2019, 2020). Importantly, several factors, including brain-based markers of neurobiological integrity, may relate to an individual's ability to consistently abstain or reduce alcohol consumption after treatment. Identification of these neurobiological markers of functional integrity may allow for early identification of individuals at the greatest risk for resuming hazardous levels of alcohol use following treatment. Accordingly, the present study examined the relationship between regional brain metabolite concentrations among individuals in the early phase of AUD treatment and posttreatment alcohol consumption levels.

The World Health Organization risk drinking levels (WHO-RDL; WHO, 2000) designate the degree of risk (mortality) associated with varying levels of alcohol consumption. Risk levels are defined by the amount of standard alcohol consumed per day (one standard drink contains 14 g of pure ethanol), with sex-specific ranges: abstinent (0 g males/females), low risk (1–40 g males/1–20 g females), medium risk (41–60 g males/21–40 g females), high risk (61–100 g males/41–60 g females), or very high risk (101+ g males/61+ g females). Recent studies demonstrated that a reduction in alcohol consumption operationalized as a change in WHO-RDL, such as reducing from high risk to medium risk, was associated with improvements in physical and mental health, psychosocial functioning, and quality of life (Knox et al., 2019, 2020; Witkiewitz et al., 2018). Similarly, lower WHO-RDL was related to reduced alcohol

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craving; this is clinically relevant because increased craving is a strong predictor of resumption of hazardous alcohol consumption posttreatment (Tuchman et al., 2024).

With respect to brain biomarkers, we previously reported that regional brain volumes near the inception of outpatient treatment were related to posttreatment WHO-RDL (Durazzo et al., 2024). Specifically, relative to light/nondrinking controls and individuals with AUD who maintained posttreatment abstinence for at least 6 months, individuals who resumed higher risk levels of alcohol use posttreatment exhibited significantly smaller cortical volumes in nodes of the executive function/cognitive control and incentive salience circuits at the onset of treatment. In contrast, individuals who resumed alcohol use at the WHO-RDL low-risk level also demonstrated smaller volumes in cortical nodes of the executive function/cognitive control and incentive salience circuits near treatment entry compared with light/nondrinking controls. However, the number of cortical regions with smaller volumes and the magnitude of these differences was less than observed for higher risk consumption. Overall, this research indicates that greater volume loss, particularly in executive function/cognitive control and incentive salience circuits, near the initiation of treatment is associated with posttreatment WHO-RDL–defined alcohol use patterns.

Several studies have demonstrated that heavy alcohol use and/or AUD is also associated with abnormalities in regional brain metabolite levels (Meyerhoff et al., 2011). Metabolites including N-acetylaspartate (NAA), myo-inositol (mI), choline-containing compounds (Cho), and creatine-containing compounds (Cr) can be measured in vivo using single-volume proton magnetic resonance spectroscopy or proton magnetic resonance spectroscopic imaging (MRSI). A recent meta-analysis (Kirkland et al., 2022) indicated that individuals with current AUD show lower NAA concentrations, a marker of neuronal integrity, in several regions, including frontal, anterior cingulate cortex, hippocampal, and cerebellar gray matter as well as frontal and parietal white matter. Similarly, Cho, a marker of cell membrane turnover/synthesis, showed lower concentrations within frontal, temporal, thalamic, and cerebellar gray matter, as well as frontal and parietal white matter. Diminished Cr levels, a marker of cellular metabolism, were observed within temporal and occipital gray matter, and higher levels were noted in midbrain gray matter. However, there were no significant differences in concentration levels of mI, a putative osmolyte and marker of astrogliosis and inflammation, between individuals with and without AUD.

Regional brain metabolite levels have also been found to be related to future alcohol consumption in those with AUD. In a sample of 20 individuals with AUD who recently achieved abstinence, lower thalamic NAA concentrations were observed among those who resumed alcohol use approximately 3 months later (Zahr et al., 2016). Significantly lower NAA and Cr levels in regions of the executive functioning and incentive salience networks at AUD treatment entry were observed in individuals who resumed any level of alcohol consumption posttreatment compared with individuals who maintained abstinence over approximately 12 months (Durazzo et al., 2010). Despite evidence that metabolite levels are associated with binary definitions of future alcohol use (i.e., abstinence vs. resumption), it is unknown if brain metabolite concentrations near treatment entry are associated with posttreatment alcohol consumption levels defined by the WHO-RDL.

The present study examined the associations between metabolite levels (NAA, Cho, Cr, and mI) in individuals with AUD near treatment entry (baseline) and WHO-RDL–defined levels of posttreatment alcohol consumption. In line with our previous studies (Durazzo et al., 2010, 2024), it was hypothesized that (a) individuals with AUD who maintain continuous abstinence posttreatment do not significantly differ from light/nondrinking controls in NAA, Cho, Cr, and mI levels at baseline in any brain region measured; (b) individuals who return to higher risk levels of alcohol consumption posttreatment exhibit significantly lower concentrations of NAA within frontal lobe gray matter and white matter at baseline compared with light/nondrinking controls and individuals with AUD who maintain abstinence; (c) individuals who return to low-risk levels of alcohol use posttreatment exhibit NAA concentrations more similar to individuals with AUD who maintain abstinence than to higher risk participants; and (d) frontal gray matter and white matter NAA concentrations are associated with characteristics of posttreatment alcohol consumption patterns in those who resume use. Findings from this study will determine if baseline regional brain metabolite concentrations are associated with WHO-RDL–defined alcohol consumption following treatment for AUD and should be considered as a viable biomarker of increased risk for resuming maladaptive levels of alcohol consumption.

Method

Participants

Data used for this examination were previously collected with approval from the Committee on Human Research of the University of California San Francisco and the San Francisco Veterans Affairs Medical Center (SFVAMC). All participants were between 28 and 70 years of age and provided written informed consent that conformed to the Declaration of Helsinki. Individuals with AUD were recruited from the SFVAMC Substance Abuse Day Hospital and the San Francisco Kaiser Permanente Chemical Dependence outpatient treatment clinics. Light/nondrinking, never-smoker, comparison subjects (light/nondrinking controls; n = 45, 13% female) were recruited from the local community via

electronic billboards. All participants were required to be fluent in English.

Treatment-seeking AUD participants (n = 85, 7% female) were required to meet diagnostic criteria for alcohol abuse or dependence according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV; American Psychiatric Association, 1994; all met criteria for dependence), consume 150/80 (male/female) standard alcohol-containing drinks per month for at least 8/6 (male/female) years before study enrollment, and not meet criteria for dependence on any other substance (excluding nicotine) in the 5 years preceding enrollment. AUD participants were allowed to have diagnoses of hepatitis C, type 2 diabetes, hypertension, unipolar mood disorders, and cigarette smoking, given the high rates of comorbidity with AUD (Durazzo et al., 2020; Gilman & Abraham, 2001; Padula & Durazzo, 2022; Stinson et al., 2005). Light/nondrinking controls (n = 45) were never-smokers with no history of biomedical and psychiatric conditions known or suspected to influence brain neurobiology and neurocognition. Light/nondrinking controls reported consuming less than or equal to 60 standard alcohol-containing drinks per month over their lifetime. Participants in this sample were included in our recent reports (Durazzo et al., 2020, 2024; May et al., 2023).

Assessments

Participants with AUD completed a comprehensive baseline assessment 16 ± 13 days after their last alcohol consumption during the early phase of outpatient treatment. Light/nondrinking controls completed a single baseline assessment. The baseline clinical assessment consisted of the Structured Clinical Interview for DSM-IV Axis I Disorders (Patient Edition, Version 2.0), the Lifetime Drinking History interview, an in-house questionnaire based on the Addiction Severity Index and National Institute on Drug Abuse Addictive Drug Survey to obtain specific information on use of other substances (type, quantity, and frequency), and self-reported anxiety (State–Trait Anxiety Inventory) and depression (Beck Depression Inventory) questionnaires. See Pennington et al. (2013) for corresponding references to the above measures.

AUD participants were classified according to their WHO-RDL–defined level of alcohol consumption posttreatment following previously described methods (see Meyerhoff & Durazzo, 2020b; Witkiewitz et al., 2017) using data collected from the Timeline Followback (Sobell & Sobell, 2000) for the posttreatment follow-up period (a minimum of 6 months). Individuals who resumed alcohol consumption at medium, high, or very high risk levels were grouped together, consistent with Durazzo et al. (2024), May et al. (2023), and Meyerhoff & Durazzo (2020b). This resulted in three separate AUD groups labeled as continuous abstainers (n = 42) or resuming to the WHO-RDL low (n = 20) or higher (n = 23) risk levels. AUD participants were also classified by smoking status as former, current, or never-smokers to examine the association of smoking status with regional metabolite concentrations, given previous demonstrations of an association between smoking status and metabolite levels in AUD (Durazzo et al., 2006, 2013).

Imaging data acquisition and processing

Structural magnetic resonance imaging and MRSI methods were thoroughly detailed previously (Durazzo et al., 2004). See Supplemental Information for detailed acquisition parameters and processing methods. (Supplemental material appears as an online-only addendum to this article on the journal's website.) Concentrations (institutional units) of NAA, Cho, Cr, and mI were obtained for the frontal, parietal, temporal gray matter and white matter, occipital white matter, and thalamus, lenticular nuclei, midbrain, and cerebellar vermis.

Statistical analyses

Demographic, substance use, and questionnaire analysis. The four groups were compared on baseline demographics (e.g., age, race), self-report questionnaires (e.g., Beck Depression Inventory, State–Trait Anxiety Inventory), and alcohol consumption variables using univariate analysis of variance and Fisher's Exact Test for categorical variables. Higher risk and low-risk groups were compared on posttreatment alcohol use variables (e.g., duration of resumption period, drinks per day, drinks per month). All statistical analyses were conducted with IBM SPSS Statistics for Windows, Version 28 (IBM Corp., Armonk, NY).

Regional metabolite concentrations. Group (abstainers, low-risk, higher risk, and light/nondrinking controls) comparisons of regional baseline NAA, Cho, Cr, and mI levels were conducted using generalized linear models and follow-up pairwise t tests. Age and body mass index (BMI) were included as covariates, given their association with MRS and MRSI-derived metabolite concentrations (Chang et al., 2009; Gazdzinski et al., 2010). Additional generalized linear models directly compared abstainers, low-risk, and higher risk participants on regional brain metabolite concentrations with age, BMI, average monthly alcohol consumed over the lifetime (higher lifetime average in higher risk), and smoking status (current, former, and never-smoker) as covariates. Smoking status (i.e., current, former, or never) was considered as a factor in comparisons between abstainers, low-risk, and higher risk participants, given previous studies showing that smoking status was associated with regional metabolite abnormalities in those seeking treatment for AUD (Durazzo et al., 2006, 2013). A modified Bonferroni procedure (Sankoh et al., 1997) was used to control for a multiplicity of tests. Group effect

Table 1. Participant demographics and clinical variables

Variable	LN (n = 45)	AB (n = 42)	RL (n = 20)	RH (n = 23)	Group comparisons
Age, *M* (*SD*)	47.6 (8.2)	51.6 (12.1)	49.7 (8.7)	51.6 (6.4)	
Education, in years, *M* (*SD*)	16.2 (2.4)	14.7 (2.3)	13.6 (1.4)	13.5 (1.5)	LN > RH, RL, RB
White, %	77.8	83.3	85	61	
Male, %	86.7	88.1	95.0	100.0	
Hollingshead socioeconomic status,[a] *M* (*SD*)	2.9 (1.8)[b]	5.5 (2.4)	6.1 (1.6)	6.5 (1.4)	
Days abstinent from alcohol at study entry	–	16 (11)	17 (17)	11 (10)	
1-year average drinks/month before study	–	380 (225)	387 (262)	500 (199)	
Lifetime average drinks/month before study	–	184 (20)	204 (29)	313 (27)	RH > RL, AB
Posttreatment follow-up interval, in days	–	238 (91)	277 (173)	398 (221)	RH > RL, AB
Days abstinent until first alcohol consumption posttreatment	–	–	158 (105)	113 (75)	
Duration of resumed alcohol use, in days	–	–	42 (62)	260 (209)	RH > RL
Drinks per day over follow-up interval, *M* (*SD*)	–	–	0.88 (0.8)	9 (6)	RH > RL
Drinks per drinking day over follow-up interval, *Mdn*	–	–	13 (10)	16 (7)	
Total drinks relapse	–	–	305 (402)	3,600 (2,568)	RH > RL
Beck Depression Inventory	4.5 (4.6)	10.7 (7.9)	12.4 (8.3)	16.8 (11.1)	RH > RL, AB > LN
State–Trait Anxiety Inventory–Trait	33.5 (8.0)	43.5 (9.8)	44.6 (10.8)	48.9 (12.1)	RH, RL, AB > LN
Depressive disorders, %	–	26.2	45.0	56.5	RH > RL > AB
Anxiety disorders, %	–	0.0	0.0	9.1	RH > RL, AB
Antidepressant use, %	–	7.1	20.0	4.3	
Never smoker, %	–	31.0	30.0	30.4	
Former smoker, %	–	16.7	5.0	13.0	
Current smoker, %	–	52.4	65.0	56.5	

Notes: LN = light/nondrinking controls; AB = abstainers; RL = low risk; RH = higher risk. [a]Lower scores indicate a higher level of occupational attainment; [b]for this analysis, n = 26.

p values for each metabolite were adjusted to account for the number of brain regions (i.e., 11) and the average Spearman inter-correlation of each specific metabolite (NAA: r = .48; Cho: r = .54; mI: r = .52; Cr: r = .57) across all participants for each region. The resulting adjusted levels for group effects were $p \leq .026$ for NAA, $p \leq .029$ for Cho, $p \leq .028$ for mI, and $p \leq .029$ for Cr (see Sankoh et al., 1997 for mathematical equations underlying this procedure and http://www.quantitativeskills.com/sisa/calculations/bonfer.htm). Significant group effects were followed up with pairwise t tests, and $p < .05$ was considered statistically significant. Partial correlations evaluated the relationship between metabolite concentrations and posttreatment alcohol use variables, with age and BMI as covariates; $p < .05$ was considered statistically significant for these analyses.

Results

Demographic, substance use, and questionnaire results

Groups were equivalent in age, sex, and race distribution but significantly differed in education, with light/nondrinking controls showing significantly higher education than the AUD groups (Table 1). Groups significantly differed on their self-reported depressive symptomatology (Beck Depression Inventory), with higher risk participants reporting higher levels than low-risk participants and abstainers; low-risk participants and abstainers did not differ from one another but reported higher levels than light/nondrinking controls. Higher risk participants also reported higher rates of a history of mood disorders (major depression or alcohol-induced mood disorder) than low-risk participants and abstainers. Groups also differed on their self-reported levels of trait anxiety, with light/nondrinking controls reporting significantly lower levels than abstainers, low-risk, and higher risk participants, who were equivalent (Table 1). Higher risk participants reported higher rates of anxiety disorders than low-risk participants and abstainers. AUD groups did not differ in the average number of drinks consumed per month in the year before the study. Higher risk participants reported a significantly higher lifetime average number of drinks consumed per month than low-risk participants and abstainers. Compared with low-risk participants, higher risk participants reported a significantly longer duration of posttreatment alcohol consumption and a higher average number of drinks consumed posttreatment. Higher risk and low-risk participants did not differ on posttreatment abstinence duration.

TABLE 2. Regional group differences in N-acetylaspartate (NAA) concentrations, *M* (*SD*), in institutional units

							Effect size (Cohen's *d*)					
Metabolite	Region	LN	AB	RL	RH	*p*	LN vs. AB	LN vs. RL	LN vs. RH	AB vs. RL	AB vs. RH	RL vs. RH
NAA	Frontal GM	32.9 (2.8)	32.0 (2.8)	30.7 (2.8)	29.7 (2.8)	<.001	0.34	0.81†	1.18‡	0.47	0.84‡	0.37
	Frontal WM	30.9 (3.0)	29.6 (2.9)	29.4 (2.9)	26.5 (2.9)	<.001	0.42	0.49	1.47‡	0.07	1.05‡	0.99‡
	Parietal WM	29.7 (3.2)	28.4 (3.2)	27.9 (3.1)	26.6 (3.1)	.003	0.41	0.54*	0.96‡	0.13	0.55*	0.42

Notes: GM = gray matter; WM = white matter; LN = light/nondrinking controls; AB = abstainers; RL = low risk; RH = higher risk.
Pairwise group comparisons are significant as follows: *$p < .05$; †$p < .005$; ‡$p \leq .001$.

Group comparisons on regional brain metabolite levels

NAA. A group effect was observed for frontal gray matter and white matter NAA concentrations (both *p*s < .001). Within frontal gray matter, higher risk participants exhibited significantly lower NAA levels than light/nondrinking controls and abstainers but did not differ from low-risk participants. Higher risk participants had significantly lower NAA concentration in frontal white matter than low-risk participants, abstainers, and light/nondrinking controls; low-risk participants, abstainers, and light/nondrinking controls were not significantly different on frontal white matter NAA (Table 2). A group effect was also seen for NAA concentration in the parietal white matter ($p = .003$), where higher risk participants showed significantly lower NAA levels than light/nondrinking controls and abstainers, and low-risk participants had a lower NAA level than light/nondrinking controls; low-risk and higher risk participants did not significantly differ on parietal white matter NAA (Table 2). A main effect for smoking status in the AUD groups was observed for frontal white matter NAA concentration ($p = .017$), where current smokers demonstrated lower NAA than never-smokers ($p = .009$); the differences between abstainers, low-risk, and higher risk participants in frontal white matter NAA remained significant after considering smoking status as a factor. Lifetime average drinks/month was not a significant predictor of any metabolite concentration in any region examined.

Cho, Cr, and mI. Groups did not significantly differ on concentrations of these metabolites in any region.

Associations of regional metabolite concentrations with posttreatment alcohol use variables

Within the combined group of higher risk and low risk, fewer posttreatment days of abstinence were associated with lower frontal gray matter ($r = .46$, $p = .003$) and white matter ($r = .47$, $p = .002$) NAA concentrations. Longer total duration of posttreatment alcohol use was related to lower frontal white matter NAA level ($r = -.41$, $p = .009$). Higher total number of drinks consumed over the posttreatment interval was associated with lower baseline frontal white matter NAA concentration ($r = -.46$, $p = .002$). Higher average number of drinks per day over the posttreatment interval was associated with lower frontal white matter NAA concentrations ($r = -.42$, $p = .008$; Figure 1).

Discussion

Numerous biopsychosocial factors contribute to the ability to engage in adaptive behaviors following treatment for AUD. The present study examined regional brain metabolites during the early phase of outpatient AUD treatment as potential biomarkers of treatment outcome as operationalized by WHO-RDLs. The main findings from this study were as follows: (a) Individuals who resumed WHO-RDL higher risk levels of alcohol consumption following treatment exhibited lower frontal white matter NAA concentrations near treatment entry than individuals who maintained abstinence and light/nondrinking controls, (b) individuals who resumed higher risk alcohol use also had lower frontal gray matter NAA concentrations than those who resumed low-risk consumption as well as abstainers and controls (all of whom did not significantly differ from one another), (c) individuals who resumed higher risk alcohol consumption posttreatment also had lower parietal white matter NAA concentrations than abstainers and controls but did not differ from individuals who resumed low-risk consumption, and (d) lower frontal gray matter and white matter NAA levels near treatment entry were associated with posttreatment alcohol consumption characteristics in the combined group of low-risk and higher risk participants.

We previously demonstrated that individuals with AUD who resumed any level of alcohol use after treatment exhibited significantly lower NAA levels near treatment entry in components of the executive function/cognitive control and incentive salience circuits (i.e., dorsolateral prefrontal cortex, anterior cingulate cortex, insula, superior corona radiata, and cerebellar vermis) compared with individuals who maintained continuous abstinence for approximately 9 months posttreatment and light-drinking controls (Durazzo et al., 2010). The current study extends these findings by demonstrating that NAA concentrations within frontal gray matter, frontal white matter, and parietal white matter at treatment entry are also associated with WHO-RDL, a more clinically salient outcome criterion than a binary definition of treatment outcome. The pattern of significantly lower NAA con-

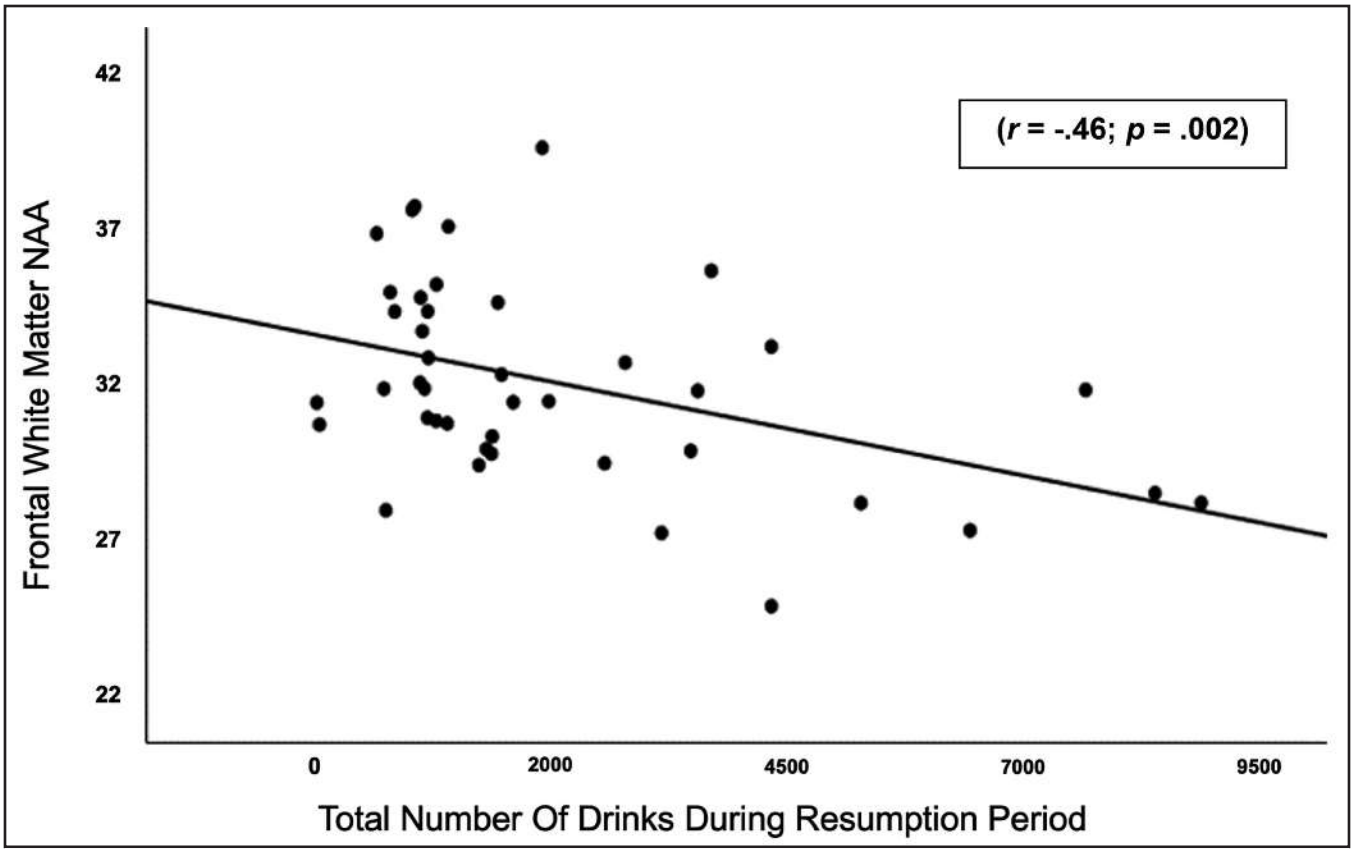

FIGURE 1. Association between the number of alcohol-containing drinks consumed during the posttreatment resumption period and frontal white matter N-acetylaspartate (NAA) concentration levels (institutional units) for combined higher risk and low risk groups.

centrations within the frontal gray matter and white matter of individuals who resumed high-risk levels of alcohol use (i.e., higher risk participants) is indicative of compromised neuronal integrity within brain regions that are central to executing several higher order cognitive processes, including decision-making, self-monitoring, and behavioral control. In addition, the associations between frontal gray matter and white matter NAA and posttreatment alcohol consumption characteristics in low-risk and higher risk participants indicate that the neuronal integrity of the frontal lobe was related to clinically relevant posttreatment behavior. Altered neuronal integrity of the frontal gray matter and white matter may confer a greater vulnerability to the cycle of resumption and remittance that affects many individuals with AUD. For example, higher risk participants may have a diminished ability, compared with low-risk participants and abstainers, to engage in the adaptive cognitive and behavioral responses requiring intact executive functions and mood regulation during treatment that are necessary to successfully maintain abstinence or reduced alcohol consumption.

In addition, pre-treatment alcohol consumption measures were not related to metabolite concentrations in the AUD groups, suggesting that the lower regional NAA levels observed in low-risk and higher risk participants were not attributable to the level of alcohol consumption before the study. Frontal white matter NAA concentrations were also related to smoking status. However, this did not account for the observed differences in WHO-RDLs, indicating that active cigarette smoking is independently associated with compromised neuronal integrity in frontal white matter within this sample of individuals with AUD. Taken together, these findings suggest that the compromised neuronal integrity of the frontal gray matter and white matter, in the early phase of treatment, predicts greater alcohol consumption for those who resume alcohol use posttreatment (Koob & Volkow, 2016; Meyerhoff & Durazzo, 2020a).

A lower concentration of NAA was also observed in parietal white matter, consistent with our previous findings of reduced cortical volume in multiple parietal regions among individuals who resumed posttreatment higher risk alcohol consumption compared with light/nondrinking controls (Durazzo et al., 2024). Given that the parietal lobe is responsible for the processing and interpretation of somatosensory information, compromised neuronal integrity within these regions, as indicated by lower NAA concentrations, may contribute to the impairments in interoception observed among individuals with AUD (Paulus & Stewart, 2014). Abnormalities in interoceptive processing are believed to

play a role in the development and course of AUD, and white matter integrity in frontoparietal regions has previously been shown to negatively correlate with activity in the insula, a critical node involved in interoceptive processing (Wi niewski et al., 2021). Therefore, greater reductions of NAA concentrations within parietal regions may serve as a biomarker of interoceptive impairments, which may place individuals at higher risk for continued maladaptive alcohol consumption posttreatment.

This study has limitations that may affect the generalizability of the results. First, these analyses were conducted within a predominantly male Veteran sample, which may limit generalizability to civilians. In addition, because of the limited number of females, potential sex effects could not be cogently investigated; however, removing the female participants from the analyses did not significantly change the results. Data were collected over a specified period during which participants already met the criteria for a diagnosis of AUD, thereby limiting our ability to examine pre-existing differences that may have predisposed some individuals to initially develop AUD or to be able to achieve reduced levels of drinking posttreatment. Metabolite concentrations were obtained at the lobar level, restricting the ability to examine the association between metabolite levels in specific cortical subregions (e.g., dorsolateral prefrontal cortex, anterior cingulate cortex) that are components of the executive and incentive salience circuits and clinical outcomes. This study primarily relied on self-report of pre- and posttreatment drinking history, substance use history, and psychiatric diagnoses and severity; however, this information was verified by medical records and collateral sources when available. Unrecorded premorbid/comorbid group differences in lifestyle or biomedical conditions (e.g., diet/nutrition, exercise, subclinical pulmonary or cardiovascular dysfunction) and genetic polymorphisms (Durazzo et al., 2023) may have influenced the results.

Future research is warranted to address these limitations and other important considerations. Because the WHO-RDL provide sex-specific cutoffs that could not be examined within our predominantly White male sample, future examinations should ensure the recruitment of a larger, more diverse sample. This could allow a more detailed examination of how NAA levels may differ as a function of biological sex and other demographic variables that may influence drinking patterns (i.e., ethnicity, nationality). In addition, research within a larger sample could also incorporate additional comparison participants that vary in terms of alcohol (e.g., lifetime abstainers) and nicotine (e.g., regular smokers without any alcohol use) use to allow for a more comprehensive examination of how varying patterns of substance use can influence NAA levels. Similarly, a larger sample could also allow for examining how the type of alcohol consumed may influence the findings. Last, in the present examination, groups differed in their report of depression and anxiety. However, these variables were not found to influence the findings. Future research should further examine whether depression and anxiety among individuals with AUD are correlated with NAA levels and examine how this may influence treatment outcomes.

Conclusion

This study demonstrated that frontal and parietal lobar NAA concentrations near treatment entry were associated with WHO-RDL categorized posttreatment alcohol consumption levels. Individuals who abstained during the follow-up period (i.e., abstainers) were not significantly different from light/nondrinking controls at baseline on any regional metabolite, indicating that intact markers of neuronal viability and cell membrane turnover/synthesis were associated with the most adaptive posttreatment consumption behavior. Frontal and parietal lobar NAA levels may serve as predictive biomarkers of clinical outcomes following treatment for AUD. Results from the current study, combined with our previous morphometric study in the same cohort (Durazzo et al., 2024), indicate that concurrent reductions of brain volume and compromised neuronal integrity of frontal and parietal lobar tissue near treatment entry are significant biomarkers that relate to clinically meaningful alcohol consumption patterns posttreatment.

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