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Regional cortical thickness recovery with extended abstinence after treatment in those with alcohol use disorder

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Abstract

Several cross-sectional investigations reported widespread cortical thinning in those with alcohol use disorder (AUD). The few longitudinal studies investigating cortical thickness changes during abstinence are limited to the first month of sobriety. Consequently, cortical thickness changes during extended abstinence in those with AUD is unclear. In this study, AUD participants were studied at approximately 1 week (n=68), 1 month (n=88) and 7.3 months (n=40) of abstinence. Forty-five never-smoking controls (CON) completed a baseline study, and 15 were reassessed after approximately 9.6 months. Participants completed magnetic resonance imaging studies at 1.5T and cortical thickness for 34 bilateral regions of interest (ROI) was quantitated with FreeSurfer. AUD demonstrated significant linear thickness increases in 25/34 ROI over 7.3 months of abstinence. The rate of change from 1 week to 1 month was greater than 1 month to 7.3 months in 19/34 ROIs. Proatherogenic conditions were associated with lower thickness recovery in anterior frontal, inferior parietal and lateral/mesial temporal regions. After 7.3 months of abstinence, AUD were statistically equivalent to CON on cortical thickness in 24/34 ROIs; the cortical thickness differences between AUD and CON in the banks superior temporal gyrus, post central, posterior cingulate, superior parietal, supramarginal and superior frontal cortices were driven by thinner cortices in AUD with proatherogenic conditions relative to CON. In actively smoking AUD,

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AUTHOR STATEMENT

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increasing pack-years was associated with decreasing thickness recovery primarily in the anterior frontal ROIs. Widespread bilateral linear cortical thickness recovery over 7.3 months of abstinence was the central finding for this AUD cohort. Proatherogenic conditions were associated with decreased thickness recovery and thinner cortex after 7.3 months of abstinence in several ROIs; this suggests alterations in perfusion or vascular integrity may relate to structural recovery in AUD. These results support the adaptive and beneficial effects of sustained sobriety on brain structural recovery in those with AUD.

Keywords

alcohol use disorder, cortical thickness; cigarette smoking; recovery; abstinence

Introduction

Cortical thickness in humans is genetically and phenotypically distinct from cortical volume and surface area (Kremen et al., 2010; Panizzon et al., 2009; Winkler et al., 2010). Cortical thickness is proposed to reflect the number and density of cells in a cortical column (Rakic, 1988, 2008) and/or neuronal cell body size, the number of spines and synapses and the extent of myelination (Eickhoff et al., 2005; Fjell & Walhovd, 2010). Cortical thickness may show a differential pattern of recovery with abstinence in alcohol use disorder (AUD) compared to volume and surface area measures in the same brain regions (Durazzo et al., 2020; Durazzo, Tosun, et al., 2011; Hutton et al., 2009; Wang et al., 2016). The cerebral cortex is primarily composed of neuronal and glial cells [i.e., astrocytes, oligodendrocytes, and microglia (Pelvig et al., 2008)], and the ratio of glial cells to neurons is approximately 0.7:1 (von Bartheld, 2018); accordingly, cortical thickness may serve as a macroscopic surrogate marker of the cytoarchitectural integrity of cells comprising the cortex (Durazzo et al., 2013; Durazzo et al., 2020; Makris et al., 2008).

Cross-sectional investigations reported widespread cortical thinning in AUD participants with variable lengths of short-term abstinence (Bae et al., 2016; Durazzo et al., 2020; Fortier et al., 2011; Grodin et al., 2017; Momenan et al., 2012; Rolland et al., 2019; Tomasi et al., 2019; Uhlmann et al., 2019; Wang et al., 2016). In treatment-seeking AUD, with approximately 1–4 weeks of abstinence, we observed that AUD participants with a comorbid proatherogenic condition (i.e., hypertension, type 2 diabetes mellitus, hepatitis C seropositivity and/or hyperlipidemia) showed greater cortical thinning in multiple bilateral mesial temporal, posterior parietal and anterior frontal regions relative to those without proatherogenic conditions and healthy controls. This magnified cortical thinning in AUD with proatherogenic conditions may relate to compromised vascular integrity, function or perfusion in affected regions. However, the AUD participants, as a group, showed extensive thinning across the cortex (Durazzo et al., 2020).

Few studies have investigated cortical thickness changes with abstinence in AUD. Wang and colleagues (Wang et al., 2016) studied individuals with AUD assessed at 1 and 14 days of sobriety and reported significant thickness increases over this interval in right hemisphere, caudal middle frontal, postcentral, superior frontal, rostral anterior cingulate, and cuneus

cortices, left hemisphere medial orbitofrontal, pars opercularis, lingual and inferior parietal area and bilateral lateral occipital and precentral cortices. Despite recovery in multiple regions, AUD participants showed thinner cortex in most areas relative to healthy controls, including the bilateral superior frontal, precentral, superior parietal and superior and inferior temporal cortices at 14 days of abstinence. Bach and colleagues (Bach et al., 2020) assessed cortical thickness in AUD participants at 12 and 27 days of abstinence and observed increased thickness in right hemisphere lateral orbitofrontal and rostral middle frontal cortices, left hemisphere insula cortex and lateral occipital cortex and bilateral superior frontal cortices. After approximately 27 days of abstinence, AUD continued to exhibit thinner cortex than controls in the paracentral cortex, superior parietal cortex, precuneus and lateral occipital cortex. Plasma leptin level appeared to mediate thickness recovery in superior frontal cortex and the insula in AUD. These longitudinal studies show similarity in the brain regions showing thickness recovery during the first month of abstinence. However, the extent of regional cortical thickness recovery over an extended period of abstinence (e.g., greater than 6 months) is unknown. Multiple studies reported more rapid recovery of cortical and subcortical brain volumes in the first 4 weeks of abstinence relative to the ensuing 6–12 months, with several regions demonstrating a non-linear trajectory [for review see (Parvaz et al., 2022) and references therein]. Assessment of thickness over extended abstinence is required to determine if there is a corresponding linear or potential non-linear change observed for regional cortical thickness and is necessary to better understand the nature and extent of human brain morphological recovery with abstinence.

The rate and magnitude of regional thickness recovery in AUD may be influenced by age, sex, comorbid medical, psychiatric, and substance use disorders, as well as chronic cigarette smoking (Durazzo et al., 2013; Durazzo et al., 2020; Salat et al., 2004; Thayer et al., 2016). Serial assessment of the influence of these variables on regional cortical thickness changes during extended sobriety will aid in the identification of the potential mediating or moderating influence of the above common comorbidities on the rate and magnitude of thickness recovery in those with AUD.

The goal of this longitudinal study was to determine the nature and extent of changes of regional cortical thickness over approximately 7.3 months of sustained abstinence in treatment-seeking AUD. Assessment after approximately 1 week, 1 month, and 7.3 months of abstinence from alcohol and illicit substances permitted a comparison of the rates of regional cortical thickness change during early abstinence (i.e., 1 week to 1 month) to changes occurring over an extended period of abstinence (i.e., 1 to 7.3 months). We specifically examined the effects of comorbid medical conditions, cigarette smoking history and psychiatric and substance use disorders on longitudinal cortical thickness changes in AUD. We predicted that:

1. In AUD, cortical thickness across the brain shows a significant linear recovery trajectory, over the three assessment points, spanning 7.3 months of abstinence.
2. The rate of regional thickness change in AUD is greater from 1 week to 1 month than from 1 to 7.3 months in all regions of interest (ROIs).

3. Abstinent AUD participants with a proatherogenic condition (Atherogenic+) show less thickness recovery than AUD without a proatherogenic condition (Atherogenic-) in anterior frontal, mesial temporal and posterior parietal ROIs over 7.3 months of abstinence.

4. Over 7.3 months of sobriety, higher pack-years in actively smoking AUD is associated with decreasing cortical thickness recovery, primarily in anterior frontal ROIs.

5. After 7.3 months of abstinence, AUD demonstrate significantly thinner regional brain volumes in anterior frontal, mesial temporal and posterior parietal ROIs compared to controls (CON). The differences between AUD and CON after 7.3 months of abstinence are driven by thinner cortices in Atherogenic+ relative to CON.

Materials and methods

Participants

AUD participants were recruited from the San Francisco VA Medical Center (SFVAMC) Substance Abuse Day Hospital and the Kaiser Permanente Chemical Dependence Recovery Program (KP) outpatient clinics in San Francisco, and CON were recruited from the Bay Area community. Ninety percent of AUD participants were from SFVAMC. The data from this study was acquired from 2001–2013. All participants provided written consent before engaging in study procedures; all procedures were approved by the SFVAMC and University of California, San Francisco and followed the of the Declaration of Helsinki. Sixty-eight (68) AUD participants were first studied after 6 ± 3 days of abstinence (assessment point 1: AP1) and 65 of those studied at AP1 were re-assessed after 34 ± 9 days of abstinence (AP2); two participants relapsed between the AP1–2 interval and data of one individual did not pass quality control standards. Twenty-three (23) AUD were enrolled in the study after approximately 4–5 weeks of abstinence from alcohol, at AP2, because they were initially treated at other facilities. Of the 88 total AUD participants studied at AP2, 48 (55%) relapsed after AP2. Of the 88 AUD studied at AP2, 40 maintained continuous abstinence from alcohol and other illicit substances for at least 4 months after AP2 and were again studied after 218 ± 44 days (approximately 7.3 months) of sobriety (AP3). Forty-five never-smoking CON completed a baseline study, and 15 were again studied after 289 ± 78 days; demographics of CON studied at baseline and follow-up were equivalent. Table 1 provides demographic and clinical data for the 88 AUD participants studied at AP2 and 45 CON at baseline.

Primary inclusion criteria for AUD participants were DSM-IV [APA (Diagnostic and statistical manual of mental disorders, 1994)] diagnosis of current alcohol dependence, fluency in English, consumption of greater than 150 alcohol-containing drinks/month (one alcohol-containing drink equivalent = 13.6 g pure ethanol) for at least 8 years before enrollment for males, and consumption of greater than 80 drinks per month for at least 6 years before enrollment for females (Meyerhoff et al., 2004). Principal exclusion criteria for AUD and CON participants are fully detailed elsewhere (Durazzo et al., 2004). CON had

no history of biomedical or psychiatric conditions suspected or known to adversely affect brain structure. In AUD, hypertension, hyperlipidemia, hepatitis C, and type-2 diabetes were permitted, as these conditions are highly prevalent in those with AUD (Durazzo et al., 2020). For AUD, current/past unipolar mood disorders (e.g., major depression) were allowed given the high comorbidity with AUD (Mertens et al., 2003; Nguyen et al., 2020). In AUD participants, dependence on any substance (other than alcohol or nicotine) within 5-years prior to study enrollment was exclusionary. Current substance abuse was allowed given the high rate of comorbid substance use disorders in AUD (Mannes et al., 2021; Stinson et al., 2005). AUD participants were assigned to never, former or active smoker groups depending on their cigarette smoking history (Durazzo & Meyerhoff, 2020).

Clinical Assessment

At their first assessment, all participants were administered the Structured Clinical Interview for DSM-IV-Axis I Disorders, Patient Edition, Version 2.0, as well as standardized questionnaires assessing anxiety (State-Trait Anxiety Inventory, for Y-2 [STAI]) and depressive (Beck Depression Inventory [BDI]) symptomatology, alcohol consumption [Lifetime Drinking History (LDH)], lifetime substance use consumption (questionnaire assessing substance type, and quantity and frequency of use based on the Addiction Severity Index and NIDA Addictive Drug Survey) and nicotine dependence via the Fagerstrom Tolerance Test for Nicotine Dependence. Average number of alcoholic drinks/month over 1 year prior to enrollment and average number of drinks/month over lifetime were calculated from the LDH. At all APs, the total number of cigarettes smoked per day and lifetime years of smoking were recorded for currently smoking AUD (there were no significant changes in cigarettes consumed over the AP1–2-3 interval for smoking AUD). Participants were screened for recent alcohol and six common illicit substances (urine toxicology), and all were negative at each AP. At AP3 for AUD, the Timeline Follow-Back Interview assessed for any alcohol or substance consumption and the quantity/frequency of any other substance use. For AUD, a comprehensive review of available electronic medical records, and/or telephone interview with collateral sources (i.e., close friends or relatives) was used to validate their abstinence/relapse status for alcohol and other substances [see (Durazzo, Tosun, et al., 2011) for specifics and references for the measures listed above]. No AUD participant in the current study consumed any alcohol or substances over the AP1–2-3 interval, as assessed via the methods described above.

AUD participants were considered positive for the substance use disorder comorbidity factor if DSM-IV criteria were met for past dependence (≥ 5 years before study participation), or current/past substance abuse; cocaine or methamphetamine abuse/dependence were the most common diagnoses. AUD were considered positive for a psychiatric comorbidity if current or lifetime DSM-IV criteria for an anxiety or unipolar mood disorder were met; the most frequent psychiatric comorbidities were major depressive disorder or substance (alcohol)-induced mood disorders, with depressive features. AUD participants who had medical record-verified proatherogenic conditions of hypertension, type 2 diabetes mellitus, hepatitis C virus antigen seropositivity and/or hyperlipidemia were assigned to the Atherogenic+ group; those without the above conditions were assigned to the Atherogenic- group (Durazzo et al., 2020); hypertension (65%) was the most frequent proatherogenic condition

and 90% of these individuals were actively using an antihypertensive medication at all APs. AUD participants seropositive for hepatitis C were not using medications to manage active symptomatology at any AP. No AUD participant had other biomedical conditions associated with atherosclerosis or other forms of vascular disease.

Magnetic Resonance (MR) Data Acquisition and Processing

A volumetric magnetization-prepared rapid gradient echo (MPRAGE) was acquired at 1.5T with TR/TE/TI = 9.7/4/300ms, 15° flip angle, 1×1 mm^2 in-plane resolution, and 1.5-mm-thick coronal partitions; see Gazdzinski and colleagues (Gazdzinski et al., 2005) for detailed MR acquisition methods. Regional brain morphometrics and intracranial volume (ICV) were quantitated with the FreeSurfer (https://surfer.nmr.mgh.harvard.edu/fswiki), via the v4.5 longitudinal pipeline (Reuter et al., 2012) from T1-weighted MPRAGE images. Images for each AP for each were processed cross-sectionally, followed by rigorous quality control and manual editing, as required (Durazzo, Mon, et al., 2011; Durazzo, Tosun, et al., 2011). An unbiased template for each participant was created for all available APs and the longitudinal processing executed in FreeSurfer (Zou et al., 2018). Average cortical thickness was obtained for the 34 bilateral cortical regions identified by FreeSurfer [see (Durazzo et al. 2020) and references therein]. Preliminary cross-sectional and longitudinal analyses showed no significant cross-sectional or longitudinal ROI differences between left and right hemisphere thickness for AUD or CON; therefore, the average of left and right hemispheres was used for each of the 34 cortical regions in all analyses (see Supplementary material Appendix 1, Fig. A1).

Analyses

Cross-sectional analyses: AUD and CON were compared on demographic and clinical variables via Fisher's Exact Test or multivariate analysis of variance. Results of cross-sectional comparisons between AUD Atherogenic+, Atherogenic- groups and CON on cortical thickness of the 34 FreeSurfer ROIs over 1-month of abstinence were previously reported (Durazzo et al., 2020); therefore, here we report the cross-sectional thickness comparisons at AP3 for AUD and follow-up for CON. Thickness comparisons between the various study groups (AUD vs. CON; Atherogenic+, vs. Atherogenic-, vs. CON; AUD never vs. AUD former vs. AUD current smoker vs. CON) at AP3 were conducted with generalized linear modeling in SPSS v28; age, treatment location (i.e., KP vs. SFVAMC; binary factor) and ICV were covariates. Main effects and interactions for all cross-sectional and longitudinal analyses were considered statistically significant at a False Discovery Rate (FDR) (Benjamini & Hochberg, 1995) of $p < .05$. Significant main effects for group were followed-up with pairwise t-tests. Effect sizes for pairwise comparisons between AUD and CON at AP3 were calculated with Cohen's *d* (Cohen, 1988).

Longitudinal analyses:

AUD Analysis I: Linear mixed modeling in R (v4.2.3) using lme4 (v1.1–32) was employed for all longitudinal analyses. Analysis I assessed for thickness change in the 34 ROIs over 7.3 months of abstinence (i.e., over AP1–2-3 interval) in AUD. In our previous studies of recovery of regional volumes (Durazzo et al., 2015; Zou et al., 2018) and neurocognition

(Durazzo et al., 2014) in the same cohort and abstinence interval used in the present report, we found both significant linear and non-linear trajectories during abstinence accurately fit the data structure. In the current study, application of our previous approach of including a non-linear term for days abstinent yielded inconsistent model convergence for some ROIs, likely yielding inaccurate parameter estimates. Consequently, we chose a more conservative approach and fit the AP1–2-3 interval with only a linear term for days abstinent for all ROIs. Random intercepts were fit for participants and final parameters were estimated with restricted maximum likelihood estimation (REML). For each ROI, age, ICV, 1-year-average drinks/month, and days abstinent were primary predictors. Proatherogenic conditions (i.e., Atherogenic+, Atherogenic-), smoking status (never, former, current), and treatment location (SFVAMC vs. KP), psychiatric, and substance abuse comorbidities (binary factors) were separately added as secondary predictors to final models.

AUD Analysis II: Rates of change (i.e., slopes) for each ROI were evaluated over the AP1-AP2 and AP2-AP3 intervals. Age, ICV, 1-year-average drinks/month, and abstinence duration served as predictors. Evaluation for differential rate of change for each ROI over AP1–2 and AP2–3 was statistically compared via linear spline analysis (Durazzo et al., 2015). Proatherogenic conditions (i.e., Atherogenic+, Atherogenic-), smoking status (never, former, current), and psychiatric, and substance abuse comorbidities (binary factors) were separately added as secondary predictors to best fitting models. Random intercepts were fit for participants and final model parameters were estimated with REML.

AUD Analysis III (smoking severity): Tested for associations between pack-years in actively smoking AUD and change in regional thickness over the AP1–2-3 interval. ROI was the dependent measure; age, abstinence duration, 1-year average drinks/month, and pack-years served as predictors. FDR was used to control for multiplicity of associations (FDR corrected $p < .05$ was considered statistically significant).

AUD vs. CON: CON had assessments at baseline and follow-up. Accordingly, comparisons of regional thickness changes among AUD and CON involved assessment over the AP1–3 interval in AUD versus change over the baseline to follow-up interval for CON. Predictors included group (AUD vs. CON), ICV, age and time (days abstinent for AUD and inter-scan interval for CON), and group x time interaction.

RESULTS

Demographics and clinical measures

See Table 1 for all comparisons between AUD and CON. Demographic and alcohol consumption variables between AUD groups studied at AP1, AP2, or AP3 were not significantly different; therefore, the data for AP2 (the largest AUD subsample) is presented in Table 1.

AUD regional cortical thickness changes over 7.3 months of abstinence

AUD Analysis I – change over the AP1–2-3 interval—Over the entire 7.3 months of abstinence, all regions except for the entorhinal, lingual, paracentral, pars triangularis,

precentral, rostral anterior cingulate, superior temporal, temporal pole, transverse temporal cortices showed significant linear recovery (see Table 2 and Figs. 1 and 2 for representative examples). No ROI showed a linear thickness decrease. Increasing age was related to decreasing thickness recovery in ROIs, except the caudal and rostral anterior cingulate, cuneus, entorhinal, insula, parahippocampal, and pericalcarine cortices. Increasing 1-year-average drinks/month was related to decreasing recovery of the pars orbitalis, pars triangularis, and supramarginal cortices. Atherogenic+ showed significantly less recovery than Atherogenic- in the caudal middle frontal, middle temporal, entorhinal, fusiform, inferior parietal and parahippocampal cortices. Smoking status, psychiatric, and substance abuse comorbidities and treatment location were not significant predictors of thickness change for any ROI. There were no significant interactions among any of the predictors for any ROI.

AUD Analysis II – cortical thickness changes for AP1-AP2 and AP2-AP3 intervals

AP1–2 interval: AUD showed significant thickness increases in all regions except the cuneus, entorhinal, frontal pole, pericalcarine, precentral, rostral anterior cingulate, and transverse temporal cortices (see Table 3). Increasing age was associated with decreasing recovery in most of the same regions indicated win Analysis I. Proatherogenic conditions, smoking status, treatment location, psychiatric, and substance abuse comorbidities were not significant predictors of thickness change for any ROI. No significant interactions were observed among any of the predictors for any ROI.

AP2–3 interval: Twelve (12) of 34 ROIs showed significantly increased thickness over the AP2–3 interval (see Table 3). Increasing age was associated with decreasing recovery in primarily the same regions reported win Analysis I. Proatherogenic conditions, smoking status, treatment location psychiatric, and substance abuse comorbidities were not significant predictors of thickness change for any ROI. There were no significant interactions among any predictors for any ROI.

AP1–2 vs. AP2–3 interval: Thickness change rate over AP1–2 was significantly greater than AP2–3 for 19 of 34 ROIs, with five showing trend levels (p = .06-.08). This indicates a potential non-linear change over the AP1–2-3 interval in 19 ROIs (see Table 3 and Fig. 3 for representative example).

AUD Analysis III – association between cigarette pack-years and thickness change over the AP1–2-3 interval for active smokers—In actively smoking AUD, increasing pack-years were linearly related to decreasing thickness recovery in 11 of 34 ROIs: caudal anterior cingulate, caudal middle frontal, entorhinal, lateral and medial orbitofrontal, paracentral, pars orbitalis, pars triangularis, pericalcarine, rostral middle frontal, superior frontal cortices.

Comparison of regional thickness changes between AUD and CON

A group (AUD vs. CON) x time interaction was seen for all ROIs (all FDR p < .05), except the cuneus, entorhinal, lateral occipital, pericalcarine, precentral and transverse temporal

cortices. In ROIs with a significant group x time interaction, AUD showed greater thickness increase than CON. No significant thickness changes were apparent for CON in any ROI.

Cross-sectional comparisons of regional cortical thickness between AUD at AP3 and CON

Since CON had no significant thickness changes, the larger baseline sample (n=45) was used in all cross-sectional comparisons to AUD. After approximately 7.3 months of sobriety, the AUD group, as a whole, showed significantly thinner cortices than CON in 10 ROIs (see Table 4). Atherogenic+ showed significantly thinner cortices than CON in the banks superior temporal gyrus, inferior parietal, insula, middle temporal, pars opercularis, post central, posterior cingulate, superior parietal, supramarginal and superior frontal cortices (all FDR $p < .05$). Atherogenic- had thinner cortex than CON on the fusiform, insula, middle temporal, and pars opercularis cortices (all FDR $p < .05$). No significant differences were observed between Atherogenic+ and Atherogenic- in any ROI. AUD smoking status groups at AP3 and CON showed no thickness differences in any ROI.

DISCUSSION

The main findings from this longitudinal investigation were: (1) Treatment-seeking AUD demonstrated significant linear (26/34 ROIs), and potential non-linear (19/34 ROIs) thickness increases in ROIs over 7.3 months of abstinence; the rates of change for AUD in the 19 ROIs were significantly greater over 1-week-to-1-month of abstinence than over 1-to-7.3-months of abstinence. (2) Atherogenic conditions were associated with lower thickness recovery in anterior frontal, inferior parietal and lateral/mesial temporal regions. (3) Cigarette smoking history, psychiatric, and substance misuse comorbidities were not significant predictors of regional thickness changes. (4) Greater alcohol consumption over the year preceding study was related to decreased recovery of the pars orbitalis, pars triangularis, supramarginal cortices; in actively smoking AUD, increasing pack-years was linearly associated with decreased thickness recovery in primarily anterior frontal ROIs. (5) After 7.3 months of abstinence, AUD were statistically equivalent to CON on cortical thickness on 24/34 ROIs; the cortical thickness differences between AUD and CON in the banks superior temporal gyrus, post central, posterior cingulate, superior parietal, supramarginal and superior frontal cortices were driven by thinner cortices in Atherogenic+ relative to CON.

The regional thickness increases over the AP1–2 interval observed in this study (27/34) were highly congruent with previous thickness recovery reported over 2–4 weeks of abstinence (Bach et al., 2020; Wang et al., 2016). Our previous work with this AUD cohort reported cortical volumes of the entire frontal, parietal and occipital lobes showed both linear and non-linear increase over 7.5-months of abstinence; rate of change in all these regions was greater during the first month of abstinence than between 1 and 7.5-months of abstinence. After 7.5 months of abstinence, AUD continued to show smaller cortical volumes than CON in the parietal and temporal lobes (Durazzo et al., 2015). In our previous report with this AUD cohort (Zou et al., 2018), we assessed for changes in FreeSurfer quantitated volumes, over approximately 7 months of abstinence, in primarily anterior frontal cortical regions implicated in the development and maintenance of AUD; we observed that volumes of the

bilateral dorsolateral prefrontal cortex, orbitofrontal cortex, and insula showed both linear and non-linear increases, and a linear increase of the anterior cingulate cortex volume; no significant volume differences in these regions were apparent between AUD and CON after approximately 7 months of abstinence. Taken together, there is strong correspondence within this AUD cohort for regions showing both bilateral cortical volume and thickness recovery over approximately 7 months of abstinence from alcohol. Given the major component of cortical volume is surface area (Im et al., 2006; Winkler et al., 2010), it is likely that linear and non-linear increases in cortical surface area are apparent in regions showing corresponding thickness and volume increases in this AUD cohort over 7-plus months of abstinence.

The differences between AUD and CON at AP3 in the banks superior temporal gyrus, post central, posterior cingulate, superior parietal, supramarginal and superior frontal cortices were driven by thinner cortices in Atherogenic+ relative to CON. At AP3, Atherogenic- only showed thinner cortex relative to CON in the fusiform, insula, middle temporal, pars opercularis cortices. In comparison to the numerous and widely distributed significant thickness reductions observed in both Atherogenic+ and Atherogenic- over the first month of abstinence (Durazzo et al., 2020), the significant recovery of these groups resulted in many fewer thickness deficits and lower magnitude differences after 7.3-months of abstinence relative to CON. The regions where Atherogenic+ thinner cortex than CON at approximately 1-month of abstinence (Durazzo et al., 2020), and at AP3 in the current study, generally correspond to the anterior and posterior watershed zones, which are located at the juncture of two non-anastomosing arterial systems without collateral irrigation. The anterior watershed zone is located between regions irrigated by the anterior cerebral artery and middle cerebral artery, and the posterior watershed zone is positioned between coverage provided by the posterior cerebral artery and middle cerebral artery (Mangla et al., 2011). Watershed zones are vulnerable to the effects of decreased perfusion pressure or cerebral blood flow, and compromised perfusion is linked to cortical thinning in those with vascular risk factors (Alosco et al., 2013; Alosco et al., 2014). Atherogenic+ showed less recovery than Atherogenic- in the entorhinal, fusiform, and parahippocampal regions. These regions demonstrate higher metabolic activity than surrounding cortical regions, and the greater metabolic demand may render these regions more susceptible to atherosclerotic-related perfusion dysfunction (Kivisaari, Probst & Taylor 2013; Stranahan & Mattson, 2010). Taken together, the diminished recovery in the aforementioned regions and the persistent regional thinning in the Atherogenic+ group observed at AP3 suggests compromised perfusion secondary to arterial/arteriole integrity and/or altered hemodynamics.

Human and animal data suggest that brain structural recovery in AUD during early and extended abstinence may be associated with increases in neuronal dendritic arbor, soma/cell volume, synaptogenesis/synaptic density, glial proliferation (particularly astrocytes and microglia), and remyelination (Crews & Nixon, 2009; Dlugos & Pentney, 1997; Fritz et al., 2019; Miguel-Hidalgo, 2018; Sullivan & Pfefferbaum, 2005). The cortical thickness and volume increases over the AP1–2 versus AP2–3 interval observed in this cohort suggest that the neuronal components (e.g., dendrites/dendritic spines, cell bodies) and glial cells (e.g., protoplasmic astrocytes), that combine to constitute the tissue mass of cortex, may recover at different rates in many regions. Several ROIs that showed greater thickness

recovery over AP1–2 relative to the AP2–3 interval are cortical nodes in functional circuits involved in salience appraisal, executive functions, mood/affect processing and regulation, self-monitoring, behavioral control and default mode (Williams, 2016). The more rapid thickness recovery in these critical functional regions during early abstinence may relate to improved integrity of functions/abilities necessary to maintain extended sobriety.

In actively smoking AUD, greater pack-years were linearly associated with decreased thickness recovery in primarily bilateral anterior frontal regions. Consistent with this association, we previously found that greater years of smoking was significantly associated with decreased recovery of frontal white matter volume (Durazzo et al., 2015). The bilateral frontal regions that showed lower thickness recovery with increasing pack-years serve as cortical nodes of circuits implicated in executive functions, mood/affect processing and regulation, self-monitoring and behavioral control (Williams, 2016), all of which have been reported to show dysfunction in active cigarette smokers (Durazzo, Meyerhoff, & Nixon, 2010). Ever accumulating evidence indicates anterior frontal regions show greater susceptibility to the adverse effects of cigarette smoking in those with and without AUD (Durazzo et al., 2014; Durazzo & Meyerhoff, 2021; Durazzo et al., 2018; Faulkner et al., 2021).

This report has limitations that may influence the generalizability of the findings. Although critical model assumptions were met in all analyses, the modest number of AUD participants at AP3, and CON at follow-up, increases risk of model over-fitting and associated Type I error. The lower number of ROIs showing significant linear recovery over the AP2–3 interval compared to the AP1–2 interval was likely related to the modest number of observations at AP3 and the corresponding reduction in power. The number of Atherogenic+ did not permit assessment of the potential individual associations of hypertension, hepatitis C seropositivity, type 2 diabetes and hyperlipidemia with regional changes in cortical thickness. The findings may have been influenced by factors not assessed in this study including exercise, pulmonary function, subclinical liver dysfunction, sleep architecture and quality and genetic predispositions (Mon et al., 2013; Zahr & Pfefferbaum, 2017). In this study, we combined comorbid psychiatric conditions into a binary variable; while this factor did not predict thickness in cross-sectional or longitudinal analyses, further consideration of the individual effects of mood, anxiety and other comorbid psychiatric conditions on cortical thickness in AUD is warranted. Assessment of the effects of biological sex were not possible due to the limited number of females (10%) in this mostly Veteran sample. Given the limited number of females in this study, the results may not generalize to females with AUD.

Results from this treatment-seeking AUD cohort indicate substantial recovery of regional cortical thickness over approximately 7.3 months of abstinence. However, there were factors associated with diminished recovery; atherogenic+ demonstrated reduced recovery in several regions and thinner cortex in a greater number of ROIs than Atherogenic- at AP3. Additionally, in active smokers, the higher pack-years was associated decreased recovery in several anterior frontal regions; this supports the importance of implementation of concurrent smoking cessation programs for active smokers seeking treatment for AUD. Further longitudinal research in larger cohorts is necessary to better understand the relationships of individual proatherogenic conditions on cortical thickness recovery in AUD.

Larger longitudinal studies are required to examine the neurocognitive and psychosocial correlates of cortical thickness recovery during sustained abstinence in AUD. Overall, this data provides clinically relevant information on the beneficial effects of sustained sobriety on human brain morphology and reinforces the adaptive effects of abstinence-based recovery in AUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SHORT OVERVIEW

- Brain cortical thickness changes over 7 months of abstinence was assessed in AUD.
- AUD demonstrated linear thickness increases in multiple increases across the cortex.
- Sustained abstinence is associated with regional cortical thickness recovery in AUD.

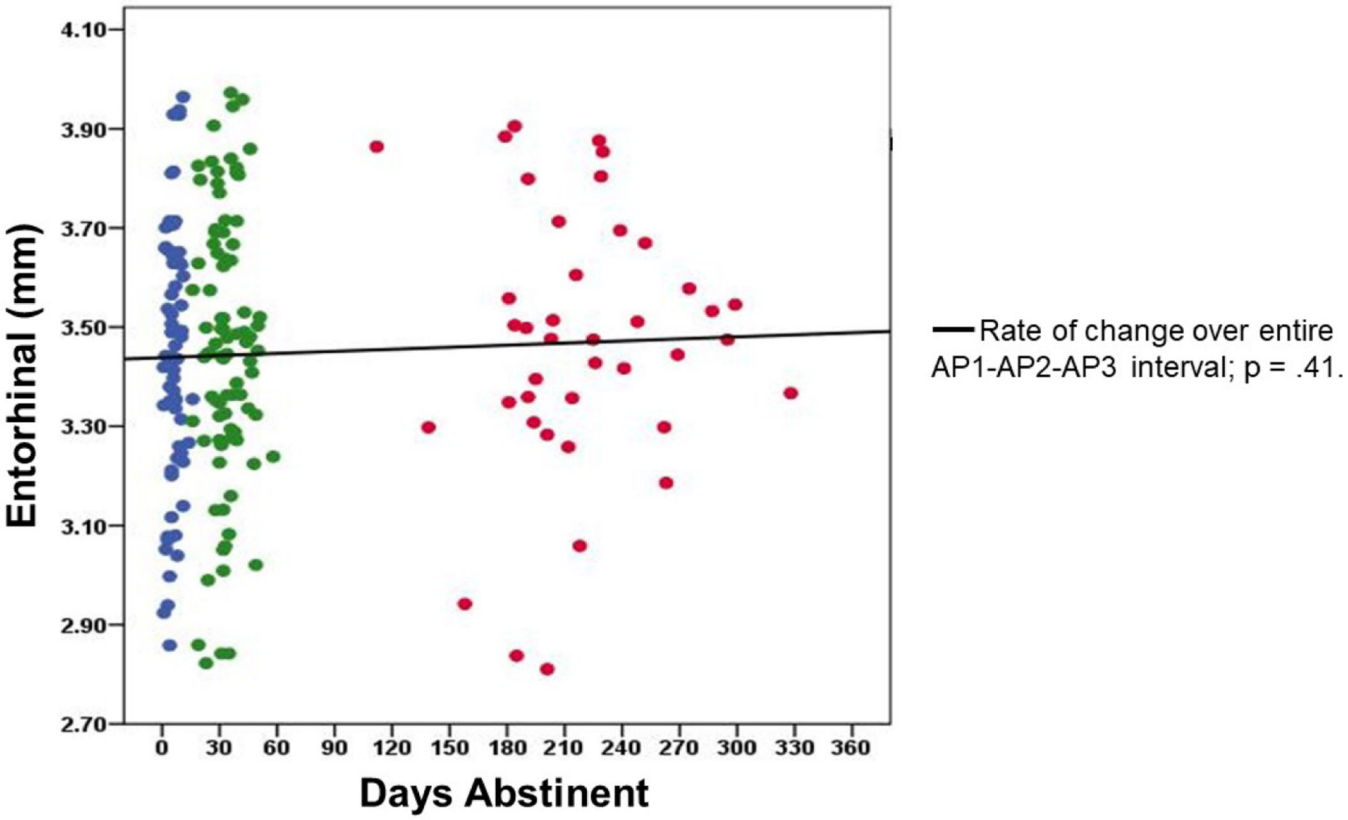

Figure 1.

Entorhinal Cortex (mm) Rate of Change over Approximately 7.3 Months of Abstinence (Assessment Point 1-2-3 Interval). Blue circles = Assessment Point 1; Green circles = Assessment Point 2; Red circles = Assessment Point 3.

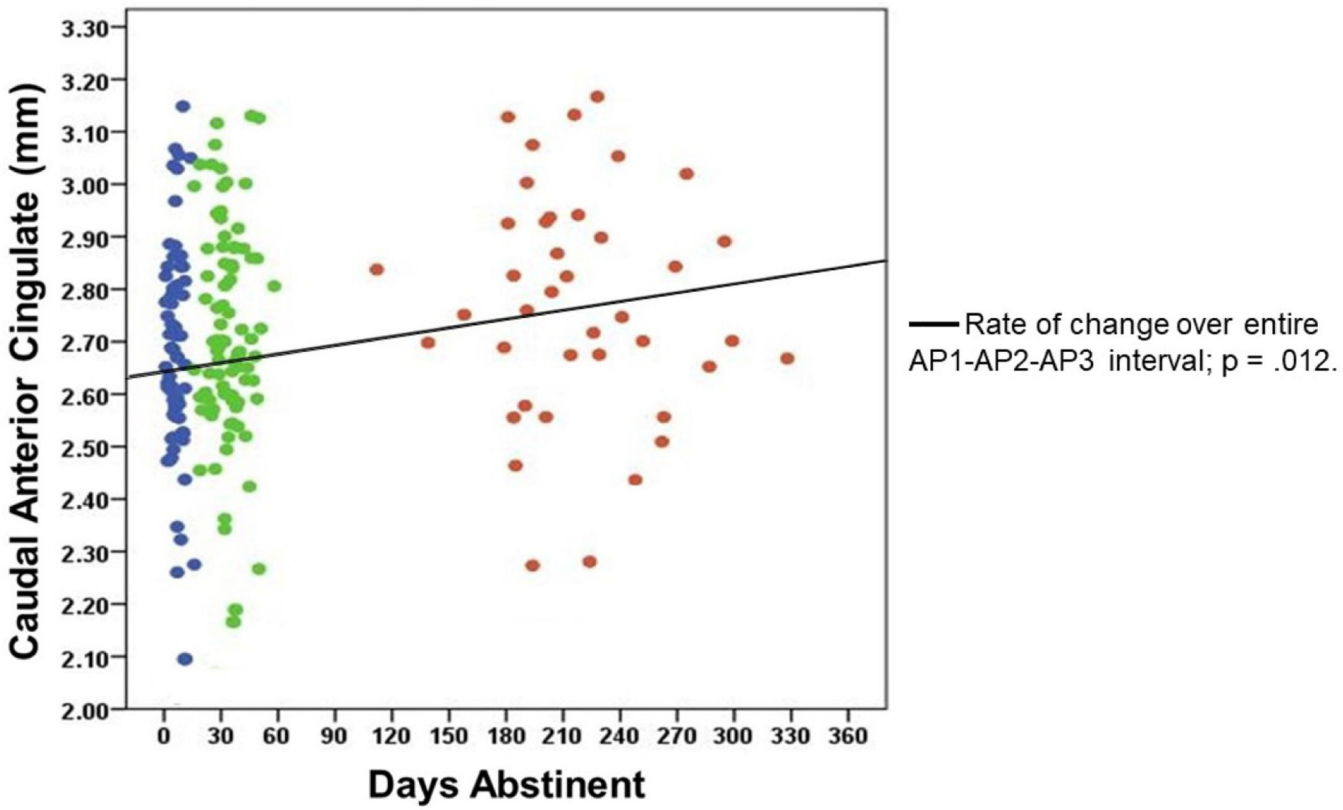

Figure 2.

Caudal Anterior Cingulate (mm) Rate of Change over Approximately 7.3 Months of Abstinence (Assessment Point 1-2-3 Interval). Blue circles = Assessment Point 1; Green circles = Assessment Point 2; Red circles = Assessment Point 3.

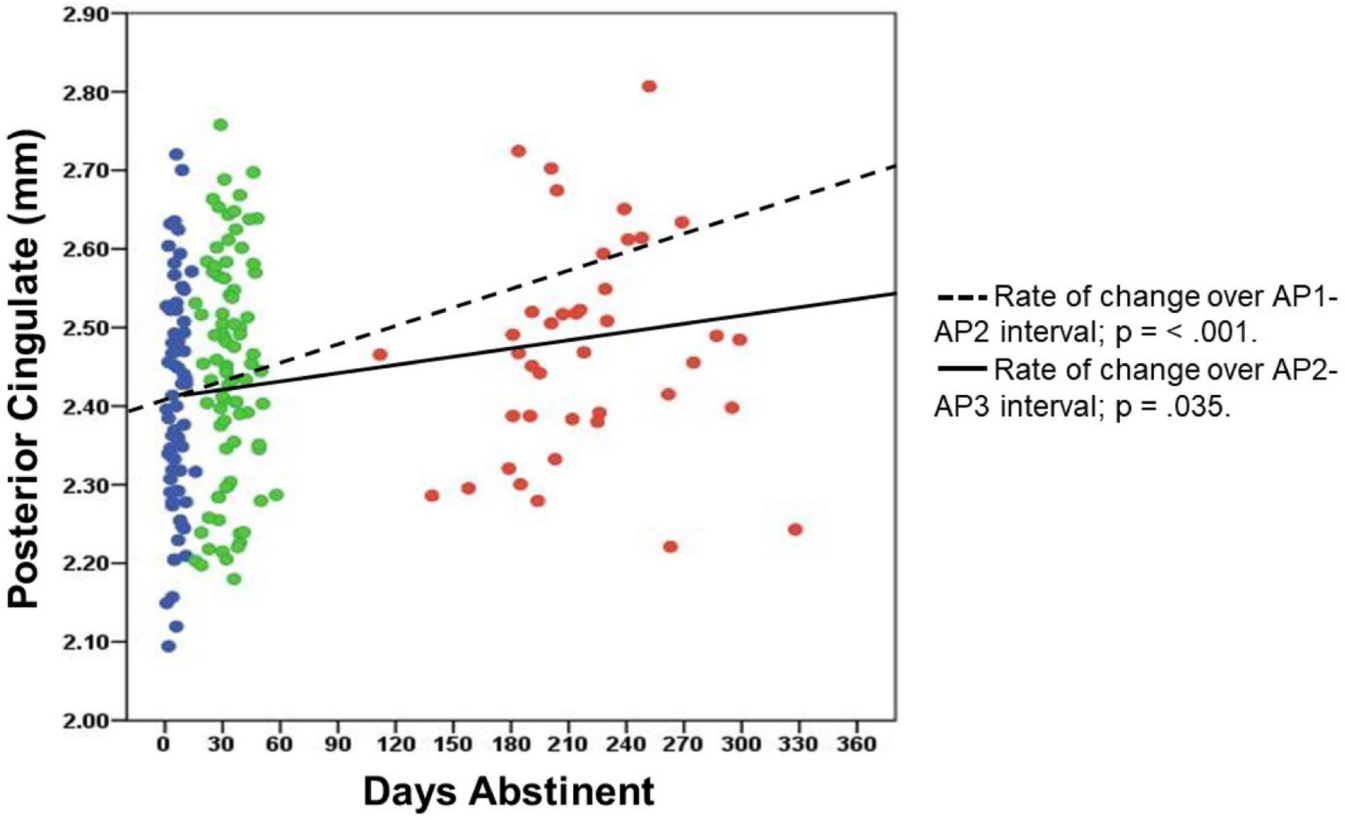

Figure 3.

Posterior Cingulate (mm) Rate of Change over Approximately 1 Week-to-1-Month versus 1-Month-to-7.3-Months of Abstinence. Blue circles = Assessment Point 1; Green circles = Assessment Point 2; Red circles = Assessment Point 3.

Table 1.

Group Demographics and Clinical Measures

Measure	CON (n = 45)	AUD (n = 88)
Days abstinent	NA	
AP1		6 (2)
AP2		33 (9)
AP3		218 (44)
Age (years)	46 (9)	51 (10)
Years of education[a]	17 (3)	14 (2)
Male (%)	90	90
Caucasian (%)	78	80
1-year average drinks/month[a]	13 (13)	397 (217)
Lifetime average drinks/month[a]	17 (16)	221 (136)
History of comorbid substance abuse/dependence (%)	NA	19
History of comorbid psychiatric disorder (%)	NA	50
History of atherogenic medical condition (%)	NA	44
AUD with history of atherogenic medical condition		
Hypertension (%)	NA	65
Hepatitis C seropositivity (%)	NA	35
Hyperlipidemia (%)	NA	19
Type 2 diabetes (%)	NA	5
Beck Depression Inventory[a]	5 (5)	14 (2)
State-Trait Anxiety Inventory-Trait[a]	38 (8)	47 (10)
Active smokers (%)	NA	53
Former smokers (%)	NA	18
Never smokers (%)	100	29
Fagerstrom Test of Nicotine Dependence (active smokers)	NA	5 (2)
Pack-years (active smokers)	NA	27 (22)

Note. Mean (standard deviation); AUD: alcohol use disorder participants; CON: non-smoking controls.

[a]AUD > CON, $p < .05$ for all group differences; NA = not applicable.

Table 2.

Linear Rates of Change for AUD in Regional Thickness over 7.3 months of Abstinence

Region	Linear		
	β days abstinent	SE	FDR p-value
Banks Superior Temporal Gyrus	1.72e-04	6.12e-05	.019
Caudal Anterior Cingulate	2.31e-04	5.95e-05	.012
Caudal Middle Frontal	1.52e-04	6.92e-05	.030
Cuneus	1.52e-04	4.87e-05	.029
Entorhinal	1.20e-05	1.03e-04	NS
Frontal Pole	2.96e-04	1.17e-04	.013
Fusiform	1.57e-04	5.38e-05	.020
Inferior Parietal	1.95e-04	4.72e-05	.007
Inferior Temporal	2.23e-04	6.69e-05	.020
Insula	2.12e-04	4.94e-05	.004
Isthmus Cingulate	2.60e-04	5.30e-05	.001
Lateral Occipital	1.20e-04	2.05e-04	.013
Lateral Orbitofrontal	2.92e-04	5.96e-05	< .001
Lingual	7.66e-05	4.08e-05	.083
Medial Orbitofrontal	2.66e-04	6.86e-05	.013
Middle Temporal	2.29e-04	7.73e-05	.015
Paracentral	1.39e-04	7.34e-05	.081
Parahippocampal	1.46e-04	6.90e-05	.047
Pars Opercularis	1.30e-04	5.76e-05	.030
Pars Orbitalis	2.64e-04	7.76e-05	.015
Pars Triangularis	1.39e-04	6.60e-05	.068
Pericalcarine	1.56e-04	6.00e-05	.016
Postcentral	1.39e-04	2.04e-04	.018
Posterior Cingulate	2.20e-04	4.88e-05	.003
Precentral	5.38e-05	7.14e-05	.45
Precuneus	1.81e-04	4.26e-05	.006
Rostral Anterior Cingulate	1.68e-04	8.60e-05	.078
Rostral Middle Frontal	2.11e-04	5.28e-05	.009
Superior Frontal	2.28e-04	5.90e-05	.010
Superior Parietal	1.49e-04	5.26e-05	.018
Superior Temporal	1.15e-04	6.64e-05	NS
Supramarginal	1.83e-04	4.97e-05	.014
Temporal Pole	2.13e-04	1.16e-04	.10
Transverse Temporal	3.93e-05	8.30e-05	NS

Note. β = slope. FDR: False Discovery Rate corrected $p < .05$ considered statistically significant (values between .05 and .10 are considered trends and values greater than .10 listed as not significant, NS). SE: standard error of the estimate.

Table 3.

Linear Rates of Change in Regional Thickness for AUD over AP1–2 and AP2–3 Intervals

Region	AP1–2			AP2–3			Difference in β AP1–2 vs. AP2–3
	β days abstinent	SE	FDR p-value	β days abstinent	SE	FDR p-value	FDR p-value[a]
Banks Superior Temporal Gyrus	9.72e-04	3.29e-04	.009	1.33e-04	7.53e-05	NS	.060
Caudal Anterior Cingulate	1.10e-03	3.35e-03	.004	1.57e-04	6.14e-05	.045	.037
Caudal Middle Frontal	1.11e-03	4.11e-04	.013	8.99e-05	6.67e-05	NS	.045
Cuneus	4.35e-04	2.88e-04	NS	1.19e-04	5.37e-05	.071	NS
Entorhinal	6.89e-04	6.30e-04	NS	6.83e-05	1.08e-04	NS	NS
Frontal Pole	1.42e-03	7.50–04	.073	2.35e-04	1.04e-04	.064	.040
Fusiform	1.34e-03	3.01e-03	.001	1.06e-04	5.44e-04	.101	.044
Inferior Parietal	9.34e-04	2.62e-04	.002	1.62e-04	4.88e-05	.034	.042
Inferior Temporal	1.24e-04	3.25e-04	<.001	1.60e-04	6.89e-05	.062	.024
Insula	9.70e-04	2.47e-04	<.001	1.54e-04	5.86e-05	.046	.042
Isthmus Cingulate	9.93e-04	2.50e-04	<.001	2.09e-04	7.71e-05	.042	.068
Lateral Occipital	1.04e-03	2.50e-03	<.001	5.56e-05	5.53e-05	NS	.028
Lateral Orbitofrontal	1.38e-03	2.70e-03	<.001	2.27e-04	7.66e-05	.041	.021
Lingual	6.05e-04	2.07e-04	.011	3.47e-05	5.00e-05	NS	.055
Medial Orbitofrontal	9.53e-04	3.75e-04	.018	1.87e-04	7.49e-05	.046	NS
Middle Temporal	1.18e-03	4.07e-04	.009	1.89e-04	7.89e-05	.057	.031
Paracentral	1.07e-04	4.19e-04	.012	1.21e-04	7.29e-05	NS	.079
Parahippocampal	1.12e-03	4.07e-04	.009	1.18e-03	4.07e-04	.035	NS
Pars Opercularis	9.44e-04	3.24e-04	<.001	7.86e-05	5.42e-05	NS	.047
Pars Orbitalis	1.96e-03	3.66e-04	<.001	1.72e-04	9.21e-05	NS	.005
Pars Triangularis	1.97e-03	3.67e-04	<.001	6.31e-05	7.42e-05	NS	.022
Pericalcarine	5.50e-04	3.51e-04	NS	1.30e-04	6.92e-05	NS	NS
Postcentral	6.78e-04	2.81e-04	.024	9.76e-05	5.12e-05	NS	NS
Posterior Cingulate	1.08e-03	2.71e-04	<.001	1.56e-04	5.41e-05	.035	.030
Precentral	5.31e-04	4.05e-04	NS	1.21e-04	7.29e-05	NS	NS
Precuneus	9.64e-04	2.19e-04	<.001	1.44e-04	4.80e-05	.041	.025
Rostral Anterior Cingulate	5.74e-04	4.62e-04	NS	1.68e-04	8.60e-05	NS	NS
Rostral Middle Frontal	1.40e-03	2.75e-04	<.001	1.35e-04	5.22e-05	.045	.005
Superior Frontal	1.04e-03	3.39e-04	.007	2.00e-04	6.41e-05	.047	.029
Superior Parietal	9.08e-04	2.90e-04	.006	1.10e-04	5.51e-05	.104	.042
Superior Temporal	9.79e-04	3.25e-04	.008	7.22e-05	6.49e-05	NS	.042
Supramarginal	7.62e-04	2.62e-04	.009	1.56e-04	5.42e-05	.030	NS
Temporal Pole	1.27e-03	5.91e-04	.045	3.82e-06	2.04e-06	NS	.066

Region	AP1–2			AP2–3			Difference in β AP1–2 vs. AP2–3
	β days abstinent	SE	FDR p-value	β days abstinent	SE	FDR p-value	FDR p-value[a]
Transverse Temporal	2.82e-04	3.65e-04	NS	1.26e-06	1.40e-06	NS	NS

Note. β = slope. FDR: False Discovery Rate corrected $p < .05$ considered statistically significant (values between .05 and .10 are considered trends and values greater than .10 listed as not significant, NS). SE: standard error of the estimate. SE: standard error of the estimate.

[a] $p < .05$ indicates rate of thickness change for AP1–2 is statistically greater than for AP2–3.

Table 4.

Regional Thickness Comparisons of CON and AUD at AP3

Region	CON (n = 40)	AUD (n = 45)	FDR p-value	Effect Size (Cohen's d)
Banks Superior Temporal Gyrus[#]	2.57 (0.11)	2.50 (0.12)	< .05	0.53
Caudal Anterior Cingulate	2.69 (0.17)	2.70 (0.16)	NS	0.09
Caudal Middle Frontal	2.51 (0.11)	2.48 (0.09)	NS	0.34
Cuneus	1.91 (0.10)	1.91 (0.11)	NS	0.01
Entorhinal	3.48 (0.24)	3.46 (0.25)	NS	0.05
Frontal Pole	2.96 (0.20)	2.87 (0.24)	NS	0.39
Fusiform[#&]	2.68 (0.11)	2.49 (0.11)	< .05	1.74
Inferior Parietal[#]	2.54 (0.11)	2.50 (0.11)	NS	0.36
Inferior Temporal	2.92 (0.11)	2.91 (0.11)	NS	0.01
Insula[#&]	3.10 (0.11)	3.02 (0.11)	< .05	0.79
Isthmus Cingulate	2.58 (0.17)	2.60 (0.17)	NS	0.12
Lateral Occipital	2.28 (0.10)	2.27 (0.10)	NS	0.06
Lateral Orbitofrontal	2.73 (0.10)	2.69 (0.10)	NS	0.40
Lingual	1.99 (0.09)	1.99 (0.09)	NS	0.06
Medial Orbitofrontal	2.58 (0.14)	2.54 (0.14)	NS	0.25
Middle Temporal[#&]	2.99 (0.12)	2.87 (0.12)	< .05	0.97
Paracentral	2.31 (0.11)	2.28 (0.11)	NS	0.25
Parahippocampal	2.74 (0.22)	2.71 (0.22)	NS	0.13
Pars Opercularis[#&]	2.60 (0.11)	2.52 (0.11)	< .05	0.71
Pars Orbitalis	2.86 (0.15)	2.80 (0.14)	NS	0.42
Pars Triangularis	2.51 (0.12)	2.49 (0.12)	NS	0.16
Pericalcarine	1.58 (0.10)	1.58 (0.10)	NS	0.02
Postcentral[#]	2.07 (0.09)	2.02 (0.09)	< .05	0.53
Posterior Cingulate	2.59 (0.11)	2.60 (0.11)	NS	0.15
Precentral[#]	2.39 (0.11)	2.33 (0.11)	< .05	0.55
Precuneus	2.38 (0.11)	2.36 (0.12)	NS	0.18
Rostral Anterior Cingulate	3.05 (0.16)	3.01 (0.17)	NS	0.27
Rostral Middle Frontal	2.44 (0.09)	2.42 (0.09)	NS	0.21
Superior Frontal[#]	2.77 (0.11)	2.71 (0.11)	< .05	0.54
Superior Parietal	2.26 (0.09)	2.22 (0.09)	NS	0.42
Superior Temporal	2.84 (0.14)	2.78 (0.14)	NS	0.41
Supramarginal[#]	2.57 (0.09)	2.52 (0.09)	< .05	0.55
Temporal Pole	3.75 (0.26)	3.70 (0.27)	NS	0.17
Transverse Temporal[#&]	2.37 (0.20)	2.26 (0.20)	< .05	0.55

Note: Mean (standard deviation). Note. FDR: False Discovery Rate corrected $p < .05$ considered statistically significant (values between .05 and .10 are considered trends and values greater than .10 listed as not significant, NS). SE: standard error of the estimate.

[#]Atherogentic+ < CON (FDR corrected $p < .05$).

[&]Atherogenic- < CON (FDR corrected $p < .05$).