





ORIGINAL ARTICLE

Links between psychopathological symptoms and cortical thickness in men with severe alcohol use disorder: A Magnetic Resonance Imaging study

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Abstract

Background: Anxiety and depression are psychopathological states frequently co-occurring with severe alcohol use disorder (SAUD). These symptoms generally disappear with abstinence but may persist in some patients, increasing the relapse risk.

Methods: The cerebral cortex thickness of 94 male patients with SAUD was correlated with symptoms of depression and anxiety, both measured at the end (2–3 weeks) of the detoxification treatment. Cortical measures were obtained using surface-based morphometry implemented with Freesurfer.

Results: Depressive symptoms were associated with reduced cortical thickness in the superior temporal gyrus of the right hemisphere. Anxiety level was correlated with lower cortical thickness in the rostral middle frontal region, inferior temporal region, and supramarginal, postcentral, superior temporal, and transverse temporal regions of the left hemisphere, as well as with a large cluster in the middle temporal region of the right hemisphere.

Conclusions: At the end of the detoxification stage, the intensity of depressive and anxiety symptoms is inversely associated with the cortical thickness of regions involved in emotions-related processes, and the persistence of the symptoms could be explained by these brain deficits.

KEYWORDS

abstinence, alcohol use disorders, anxiety, cortical thickness, depression

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1 | INTRODUCTION

The brain, like most organs, is vulnerable to damage from excessive alcohol consumption. A large body of evidence documents damages to the peripheral and central nervous system in individuals with severe alcohol use disorder (SAUD).¹⁻³

An accelerated global shrinkage (i.e., atrophy) of the brain is one of the most common findings in neuroimaging, with repeated observations of white and gray matter reduction, particularly in the cerebellum, insula, and frontal/temporal regions.⁴⁻⁸

One way to explore these brain changes is to measure cortical thickness (CT). CT corresponds to the metric distance between corresponding points located on the pial and white matter boundaries of the neocortex. It ranges from 1 to 4.5 mm depending on brain regions with an average of about 2.5 mm, and is part of cortical volume, together with cortical surface area and degree of gyrification.^{9,10} A reduction in CT has been observed with sustained alcohol abuse¹¹⁻¹⁵ and has been associated with relapse.¹²

At a behavioral level, SAUD is often accompanied by depressive and anxious symptoms.¹⁶⁻¹⁸ Some authors explain this association by the self-medication hypothesis asserting that alcohol may alleviate unpleasant or negative mood states.¹⁹⁻²¹ A better understanding of comorbid mood disorders is particularly important for SAUD patients attempting to quit, as they may increase relapse risk. Patients reporting high depressive/anxiety symptoms in addition to SAUD may have specific structural damage and answers may be found through exploration of neurological correlates of mood disorders in these patients.

Structural deficiencies and alterations in CT have been widely described in mood disorders. Studies of major depressive disorders, generalized anxiety disorder, and social anxiety (Kühn et al., 2011; Abdallah et al., 2012; Syal et al., 2012; Frick et al., 2013; Strawn et al., 2014; Molent et al., 2018; Suh et al., 2019) have reported frontal and temporal neuroanatomical alterations.²²⁻²⁸

Very few studies have assessed the structural brain-imaging substrates of mood collateral symptoms in patients with SAUD. Two brain imaging studies have addressed the comparison between SAUD patients with and without another established psychiatric diagnosis.^{29,30} These studies only considered diagnosed psychopathological comorbidities, thus offering no insights into the influence of the more common subclinical depression or anxious states (i.e., mild or moderate symptoms without a formal psychiatric diagnosis).

The present study aims to measure cortical ribbon thickness in a population of SAUD patients in relation to depressive and anxious symptoms measured during the detoxification phase. This phase is of particular importance: inpatients with high levels of depressive and/or anxiety symptoms at the beginning of detoxification often experience a sharp decline in symptoms within 2–4 weeks of abstinence.³¹⁻³⁶ A minority of patients however have persistent symptoms. Our aim is therefore to explore the cerebral correlates of the intensity of mood-related symptoms presented at the end of the detoxification program, namely 2–3 weeks after the day of admission. Based on the available findings in SAUD and demonstrated cortical

thinning in mood disorders, we expect to find substantial thickness reductions associated with comorbidities.

Previous studies have taken a dichotomous approach in focusing on the presence or absence of diagnoses of depression and anxiety, based on the ICD-10 or the Diagnostic and Statistical Manual of Mental Disorders (DSM, American Psychiatric Association, 2001).³⁷ Such an approach, however, does not reflect the clinical reality, in which mood disturbances should be placed on a continuum of severity rather than on a dichotomy, even low or moderate psychopathological symptoms being potentially related to brain impairments. In this study, therefore, we chose to study symptoms' intensity rather than the presence of a comorbid diagnosis.

2 | MATERIALS AND METHODS

2.1 | Participants

We recruited 94 individuals with SAUD from the full-time alcohol detoxification unit of the Cliniques Universitaires Saint-Luc, Brussels, Belgium. Patients had abstained from alcohol consumption for 14–18 days before being tested. Inclusion criteria were to meet the DSM-5 criteria for SAUD, based on the clinical assessment of the principal investigator (PDT) and being fluent in French. Exclusion criteria consisted of having history of addictive, psychiatric, neurological, or physical disorder that could influence brain morphology except for nicotine dependence. Participants could also not have a contraindication for magnetic resonance imaging (MRI). All participants gave a written informed consent. The present study is based on a reanalysis of data collected previously and that have already given rise to other publications, unrelated to the topic of the current one.³⁸⁻⁴⁰

2.2 | MR data acquisition and processing

Three-dimensional anatomical heavily T1-weighted images were acquired from a 3T Achieva, Philips Healthcare scanner with a 32-channel phased array head coil. Patients, instructed to remain still, were positioned comfortably in the coil and fitted with soft earplugs. The 3D sequence consisted of a gradient echo sequence with an inversion prepulse (Turbo Field Echo) acquired in the sagittal plane using the following parameters: TR/TE/flip angle = 9.1 ms/4.6 ms/8°, 150 slices, slice thickness = 1 mm, in-plane resolution = $0.81 \times 0.95 \text{ mm}^2$ (acquisition) reconstructed in $0.75 \times 0.75 \text{ mm}^2$, FOV = $220 \times 197 \text{ mm}^2$, acquisition matrix = 296×247 (reconstruction 3202), SENSE factor = 1.5 (parallel imaging). The whole brain was measured and segmented by completing the FreeSurfer image analysis pipeline (<http://surfer.nmr.mgh.harvard.edu>) using a set of automated sequences to reconstruct the cortical surface. The final segmentation (i.e., morphology and surface data) is based on both a subject-independent probabilistic atlas and subject-specific measured values. The atlas



is built from a training set comprising a set of 40 participants whose brains (surfaces or volumes) were labeled by hand (Dale et al. 1999; Fischl et al., 2002, 2004).⁴¹⁻⁴³ After completion of the pipeline, each segmentation was visually inspected, and any geometric inaccuracies were corrected. Only small skull strip errors were found and corrected before running the data through the pipeline again.

2.3 | Measurement of depressive and anxious symptoms

Depression was assessed with the French translation of the abbreviated version of the Beck Depression Inventory (BDI). It is a 13-item form (Beck and Beck, 1972), with each item having four option responses, scored 0, 1, 2, or 3.⁴⁴ The item's content includes sadness, pessimism, sense of failure, dissatisfaction, guilt, self-dislike, self-harm, social withdrawal, indecisiveness, distorted body image, work difficulty, fatigue, and loss of appetite. The patient score is the sum of the score obtained to each item. Higher scores indicate greater depressive severity. It is recommended to use the cutoff score of 9 to detect patients with high levels of depressive symptoms.⁴⁵

To measure anxiety, we used the State-Trait Anxiety Inventory (STAI; (Spielberger, 1983)⁴⁶; for the French version, (Bruchon-Schweitzer and Paulhan, 1993).⁴⁷ It is a self-reported questionnaire divided into two 20-item subsections measuring state and trait anxiety, respectively. Each item has four option responses, scored 1, 2, 3, or 4. We only used the state subsection (how one feels at the moment) in this study. Higher scores indicate greater anxiety severity. A threshold score of 40 is generally used to determine a clinical level of anxiety.⁴⁸

2.4 | Statistical analyses

Descriptive statistics are presented as the mean \pm SD. We used Pearson's correlation coefficient to measure the linear association between depression and anxiety scores. Whole brain analyses were undertaken using a GLM to identify the brain regions for which cortical thickness were significantly associated with depression and anxiety. FreeSurfer's Qdec was used to perform correlations between cortical thickness and depression and anxiety-related symptoms' scores with age being controlled as covariate. All results were corrected for multiple comparisons using a Monte Carlo simulation thresholded at 1.3 ($p < 0.05$).

3 | RESULTS

3.1 | Clinico-demographics

The 94 participants were men with a mean age of 47.3 ± 11.2 , a mean depression score of 7.5 ± 5.7 and a mean anxiety score of 39.4 ± 12.8 . 35% ($N = 33$) of patients showed scores above the cutoff score for

depression and 44% ($N = 41$) showed scores above the cutoff score for anxiety. We found a significant positive correlation between scores of anxiety and depression ($r = 0.661$, $p < 0.001$) (see Figure 1).

3.2 | Surface-based analyses

3.2.1 | Correlation between cortical thickness and depression

In the right hemisphere, cortical thickness was significantly and negatively associated with depression in a large cluster in the superior temporal area, with a temporal peak and going through the transverse area (see Figure 2 and Table 1). No significant correlation was found between cortical thickness and depression in the left hemisphere.

3.2.2 | Correlation between cortical thickness and anxiety

In the right hemisphere, cortical thickness was significantly and negatively linked with anxiety in a large cluster in the middle temporal area going from the supramarginal through the superior temporal and transverse with part of the middle pole and temporal pole (see Figure 3 and Table 1). In the left hemisphere, cortical thickness significantly and negatively correlated with anxiety in three regions: (1) the rostral middle frontal region with the pars opercularis, orbitalis and triangularis, (2) the inferior temporal region with mostly the gyrus fusiform lingual and the parahippocampic region, (3) the supramarginal, post-central, superior temporal, transversal temporal area (see Figure 4 and Table 1).

4 | DISCUSSION

We examined the cerebral correlates of the degree of depression and anxiety-related symptoms presented 2 weeks after detoxification admission day among patients with SAUD.

Firstly, we confirmed that most patients, at the end of the detoxification stage, presented sub-clinical levels of depression and anxiety. It should be noted that the assessment and MRI were performed between days 14 and 18, when the patients were not any longer under the effects of benzodiazepines but had already received at least 5/6 sessions of brief psychodynamic psychotherapy.⁴⁹ It is likely that these interventions contributed to improvements in symptomatology. We also observed a strong correlation between the reported anxiety and depression levels. This relationship was not surprising as symptoms of anxiety and depression often coexist.⁵⁰ High rates of comorbidity between anxiety and depressive disorders have been explained in several ways including the fact that symptoms of depression and anxiety represent different outward manifestations of the same

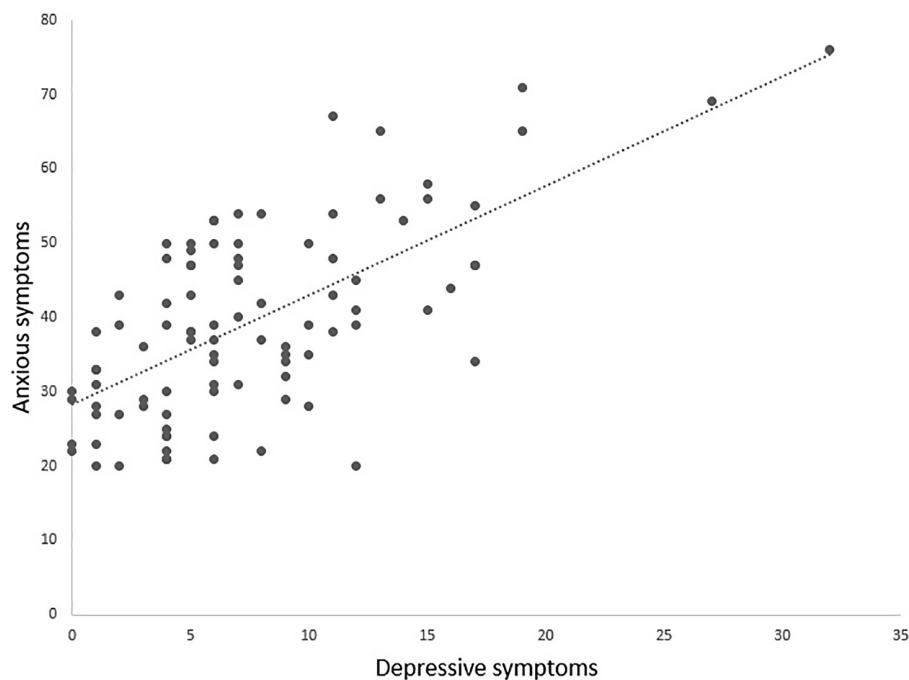


FIGURE 1 Scatter plot of anxiety scores [State-Trait Anxiety Inventory (STAI)] by depression scores [the Beck Depression Inventory (BDI)].

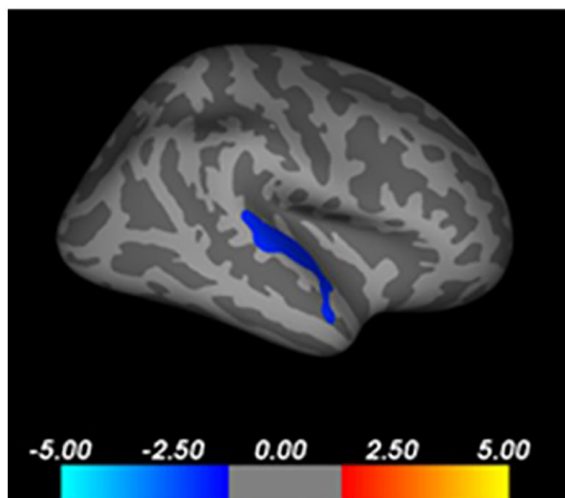


FIGURE 2 Brain areas of the right hemisphere in which cortical thickness was found negatively correlated with the current level of depression. Correction for multiple comparisons using Monte Carlo simulation ($p < 0.05$).

underlying cause⁵¹ or that anxiety may predispose to depression and vice versa.⁵²

At the brain level, we firstly observed that, in the right hemisphere, the higher the score in depressive symptoms measured by the Beck Depression Inventory, the thinner the cortical ribbon in the superior temporal gyrus. Numerous studies have shown that this region of the brain, centrally linked to emotional processing, shows morphological changes in patients suffering from major depression (MDD).^{53,54} Takahashi et al.⁵⁵ in particular, have shown that its

volume is inversely correlated with the score at the Beck Depression Inventory in MDD patients. At the functional level, Yang et al.⁵⁶ found that patients with MDD exhibit weaker neural responses to rewards in the superior temporal gyrus than healthy controls. The correlation only found with the right hemisphere is consistent with the dominance of this hemisphere in the processing of unconscious negative emotions which has long been described in the neuropsychological and neuroimaging literature.⁵⁷⁻⁶⁰ A cortical thinning of the lateral aspect of the right hemisphere has even been proposed as an endophenotype for MDD by Peterson and Weissman.⁶¹ Specifically as regard to the superior temporal gyrus, its reduced volume only in the right hemisphere has been linked to suicide in various psychiatric disorders⁶² and in particular in adolescents with MDD or resistant depression with a history of suicide attempts.^{63,64} The latter authors suggested that a reduced volume of the right superior temporal gyrus could constitute a structural neural marker of abnormalities in the evaluation of socio-emotional information.

The intensity of reported anxious symptoms was related to CT in four different brain areas. In the left hemisphere, 1-the rostral middle frontal region with the pars opercularis, orbitalis and triangularis, 2-the inferior temporal region with mostly the gyrus fusiform lingual and the parahippocampic region and 3-a region including the supramarginal, post-central, superior temporal, and transversal temporal regions. In the right hemisphere, it was associated with a cluster in the middle temporal area going from the supramarginal through the superior temporal and transverse with part of the middle pole and temporal pole.

In addition to the previously mentioned role of the superior area of the temporal pole in emotion regulation, these are the same regions that are engaged in tasks related to Theory of Mind (ToM)



TABLE 1 Cortical thickness brain areas associated with depression and anxiety in SAUD subjects.

Variables	Max ^b	Size (mm) ^c	Talairach coordinates ^a			Brain area
			X	Y	Z	
Anxiety	-2.530	1436	35	-2	-23	Right middle temporal
	-3.98	1424	-42.5	-54.6	-18.8	Left inferior temporal
	-3.275	908	-53.8	21.4	16.7	Left rostral middle frontal
	-3.058	1159	-57.6	-26.3	27.4	Left supramarginal
Depression	-2.960	1056	65.2	-17	3	Right superior temporal

^aThe Talairach coordinates of the maximum.

^bThe maximum $-\log_{10}(p \text{ value})$ in the cluster. The $-$ sign is because the correlation is negative.

^cSurface area (mm) of the cluster.

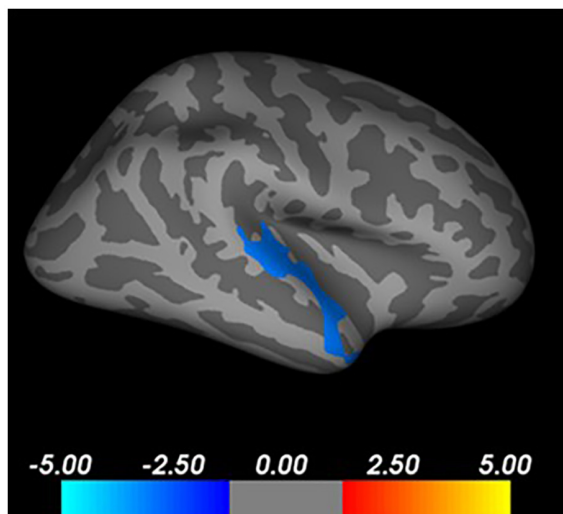


FIGURE 3 Brain areas of the right hemisphere in which cortical thickness was found negatively correlated with the current level of anxiety. Correction for multiple comparisons using Monte Carlo simulation ($p < 0.05$).

(for reviews, see Ref. [65–68]), that is, the ability to attribute mental states to other people. fMRI studies have shown that ToM demanding tasks are linked to activation of the prefrontal cortex (MPFC), temporo-parietal junction (TPJ) (an area at the border of parietal and posterior temporal lobes), superior temporal sulcus as well as temporal poles and amygdala.⁶⁹ Studies conducted in people with SAUD have shown impairments in ToM abilities⁷⁰ leading to a reduction in the quality of social interactions.^{71–73} These difficulties could underlie the phenomenon of self-medication with alcohol in SAUD individuals when confronted with negative affect and sensitive interpersonal situations.⁷⁴

In conclusion, our study shows that at the end of the detoxification stage, the intensity of depressive and anxiety symptoms is associated with reduced cortical thickness of regions involved in emotions-related processes. It suggests that in the minority of patients in whom depressive and anxious symptoms persist, alterations in cortical thickness are observed and these alterations are located in exactly the same regions as those found in patients suffering from

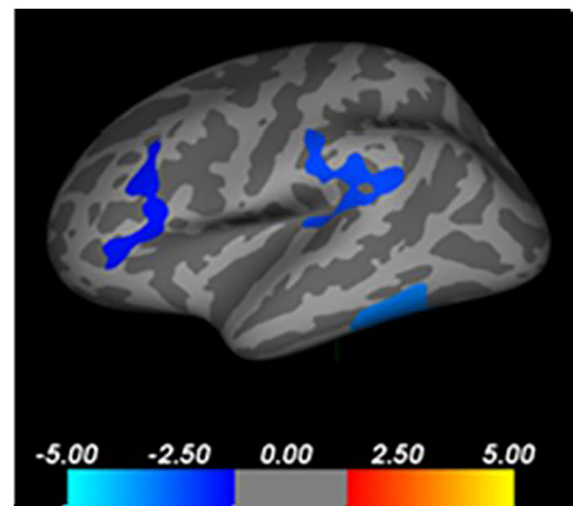


FIGURE 4 Brain areas of the left hemisphere in which cortical thickness was found negatively correlated with the current level of anxiety. Correction for multiple comparisons using Monte Carlo simulation ($p < 0.05$).

severe depression or anxiety alone. This could mean that anxiety and depressive symptoms are transient and not associated with brain changes in the majority of SAUD patients but those in whom symptoms persist present brain alterations in regions known to be impacted in individuals with a diagnosis of depression and/or anxiety.

An important limitation of our study is that we did not have data for all participants on indices of SAUD severity, which prevented us from controlling for this variable in the correlations and should be considered for future studies. The cross-sectional nature of our study does not allow to draw any conclusions on the temporality of the links, but it can be hypothesized that regardless of the origin of the cortical thinning, the improvement in anxiety and depression after detoxification may be impeded by brain deficits in these regions.

For future studies, it would be interesting to conduct a multishell diffusion or DTI study on the anatomical connections between the regions we have highlighted and the limbic regions, known as a hub of emotional processing. In particular, the uncinate fasciculus, a major tract connecting the rostral part of the prefrontal cortex (PFC)

to the amygdala,⁷⁵ is associated with the processing of emotional expressions⁷⁶ and its abnormalities have been associated with several psychiatric disorders.⁷⁷ Its exact function remains poorly understood, however, and deserves further investigation in the context of alcohol-related emotional disorders.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. GP, PdT, and PM drafted the work, and all authors revised it critically for important intellectual content. All authors gave final approval of the version to be published, and all authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

Authors do not have any conflict of interest.

DATA AVAILABILITY STATEMENT

The dataset for this manuscript is not publicly available because the data used are from different experimenters without sharing agreement and because consent had only been obtained from participants for participation in the study and not to share data with third parties. MRI data are person-specific and therefore are not anonymous. However, the cortical thickness files by region (i.e., Destrieux and Desikan-Killiany Atlases) can be made available upon request depending on the situation and after consultation and approval by the other investigators and parties involved.

ETHICS STATEMENT

Approval of the research protocol by an Institutional Reviewer Board: The protocol for this research project was submitted to and approved by the Biomedical Ethics Commission of the Université Catholique de Louvain (Belgium) and it conforms to the provisions of the Declaration of Helsinki.

Informed consent: All informed consent was obtained from the subjects before engaging in the experimental procedures.

Registry and the Registration No. of the Study/Trial: N/A.

Animal Studies: N/A.

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