THE TURKISH JOURNAL ON ADDICTIONS
www.addicta.com.tr

ORIGINAL ARTICLE

Brain Reward System and Its Volumetric Investigations in Alcohol Addiction

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Main Points

- Hippocampal volume is decreased in patients with AUD.
- Nucleus accumbens volume is decreased in patients with AUD.
- Degeneration in the brain may be effective in the continuation of addiction in patients with AUD.

Abstract

It has been shown that structural changes occur in the brain in many types of addiction and can have an impact on maintaining addictive behavior, which can be improved with treatment. The study aimed to identify structural changes in the brain's reward system in alcohol use disorder. Structural magnetic resonance imaging was employed to compare the volumes of total white matter and gray matter, as well as those of the nucleus accumbens, ventral tegmental area, amygdala, and hippocampus between 15 individuals diagnosed with alcohol use disorder and 17 healthy controls. The Michigan Alcoholism Screening Test, Severity of Alcohol Dependence Questionnaire, and Alcohol Use Disorders Identification Test were administered to the participants to reveal the pattern of alcohol use and severity of dependence. The group with alcohol use disorder exhibited a significant decrease in the volume of the right hippocampus. No differences were found between the two groups in terms of other brain regions. In conclusion, this study revealed a decrease in hippocampal volume in patients with alcohol use disorder. It is an indication that structural changes play a role in the etiology of cognitive impairments commonly seen in alcohol use disorder.
Keywords: Alcohol, brain reward system, neuroimaging, mesocorticolimbic system

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Received: April 28, 2024
Revision Requested: October 31, 2024
Last Revision Received: November 6, 2024
Accepted: November 29, 2024
Publication Date: December 27, 2024

Introduction

The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) defines alcohol use disorder (AUD) as having at least two of the 11 core symptoms for at least 12 months. A notable clinical hallmark is the pattern of frequent and larger-than-intended drinking, which is commonly combined with robust but futile attempts to quit alcohol use (APA, 2013). Alcohol use disorder is seen all over the world and often in developed countries. Genetic, psychosocial, and environmental factors are effective in the development of AUD (Kramer et al., 2020).

Structural brain changes in AUD have long been a topic of interest and research. There are both structural and functional studies of many regions, from total gray and white brain volume to the subcortical and limbic systems (Fritz et al., 2022). The fact that the ventral tegmental area (VTA) is associated with rewarding and reinforcing stimuli as well as aversion is sufficient to understand its role in addiction (You et al., 2018). Due to the variability of cell

Cite this article as: Tabara, M.F., Atmaca, M., Yıldırım, H., Solmaz, O., Amir Essibayi, M., & Gurok, M.G. (2024). Brain reward system and its volumetric investigations in alcohol addiction. *Addicta: The Turkish Journal on Addictions*, 11(3), 241-248.

populations within the VTA, which differ in their anatomical and neurochemical properties, it is difficult to identify the VTA as a whole from MR images (Morales & Margolis, 2017; Trutti et al., 2019). Most studies of the VTA are cue-related functional studies and animal studies (Avegno et al., 2021; Ilari et al., 2022). The small number of neuroimaging studies on the VTA was one of the factors that prompted us to conduct this study.

In animal and human models of AUD, the nucleus accumbens (NAc) has been identified as a critical area. Several prior studies have found that exposure to alcohol cues enhances brain activation in the NAc (Schacht et al., 2013). The NAc is thought to be associated with craving, relapse, and anticipation of drug response (Bach et al., 2015, 2021; Bracht et al., 2021). This active role of the NAc in AUD has led to the discovery of novel treatment modalities that target this region (Bach et al., 2023). In the literature on volumetric changes of the NAc, although there are mostly studies suggesting that its volume decreases, the fact that there are also findings that it does not change or even increases can be taken as evidence that more studies are needed on this subject (Bracht et al., 2021; Grodin & Momenan, 2017; Howell et al., 2013; Sousa et al., 2020; Sullivan et al., 2005).

In human functional MRI studies, the amygdala has been implicated in four things: the evaluation of positive and negative stimuli, the anticipation of reward and loss, the evaluation of reward representations by predictive cues, and the processing of alcohol-related cues in alcohol-dependent individuals (Wrase et al., 2008). The amygdala is associated with anxiety and negative urgency in AUD (Tomasi et al., 2021). Numerous studies have shown that the volume of the amygdala is reduced in alcoholics (Benegal et al., 2007; Fein et al., 2006; Grace et al., 2021; Hill, 2004). White proposed that unique components of drug-related memories are encoded in the hippocampus, dorsal striatum, and amygdala (White, 1996). The hippocampus codes explicit knowledge about cue-event relations (i.e., stimulus-stimulus associations) in alcohol-related contexts. The hippocampus plays a crucial role in processing information that guides behavioral responses to obtain alcohol reinforcement. Alcohol has the potential to bolster its own consumption by augmenting the consolidation of alcohol-related memories stored in the hippocampus, amygdala, and dorsal striatum (Goodman & Packard, 2016). Alcohol consumption has been shown to accelerate aging in the hippocampus and other subcortical regions (Tomasi et al., 2021). There are reports in the literature that hippocampal volume decreases not only in addiction but also in problematic alcohol use (Wilson et al., 2017). In addition to the regions mentioned above, alcohol-induced volumetric reductions have been reported in many other regions (Atmaca et al., 2023; Gurok et al., 2023; Tabara et al., 2024).

Existing clinical gaps in the literature on AUD include limited comprehensive studies on the structural brain changes within the reward system, particularly the variability in findings on specific brain regions such as the nucleus accumbens, VTA, amygdala, and hippocampus. While prior research has shown some associations between AUD and decreased volumes in these areas, results have been inconsistent. This may stem from variations in sample sizes, neuroimaging techniques, or patient characteristics, including treatment status and duration of abstinence. Additionally, the VTA has been underexplored due to its complex anatomical structure, leading to challenges in achieving precise volumetric measurements. This research addresses these gaps by providing a focused analysis of structural changes within the reward system in individuals with AUD compared to healthy controls, using high-resolution MRI. By including multiple regions within the reward system and ensuring reliable volumetric measurements, this study adds specificity and clarity to our understanding of the structural alterations in AUD.

The purpose of this research is to identify structural changes in the brain's reward system associated with AUD. By using structural MRI, the study aims to compare the brain volumes of specific regions involved in reward processing—such as the nucleus accumbens, VTA, amygdala, and hippocampus—between individuals diagnosed with AUD and healthy controls.

Material and Methods

Study Design

This is a cross-sectional case-control study that compares patients diagnosed with AUD to healthy controls. Approval for the study was obtained from the Fırat University School of Medicine Local Ethics Committee (Approval no: 2020/02-11), and all procedures adhered to the principles outlined in the Helsinki Declaration of 1975, as revised in 1983. The study was funded by FUBAP (Firat University Scientific Research Projects).

Participants

The patients were selected from inpatient settings. Magnetic resonance imaging (MRI) scans were performed after the detoxification process. The inclusion criteria for the cases were being between the ages of 18 and 65, meeting the diagnostic criteria for AUD according to DSM-5, absence of mental retardation or any other psychiatric disease other than AUD, absence of any systemic or organic disease, and providing written consent to participate in the study. The case group's exclusion criteria included being younger than 18 or older than 65, not having the mental capacity to comprehend and complete the rating scales, not providing signed, written informed consent, being illiterate, having a medical condition that would make imaging inappropriate, having a systemic illness that might affect the anatomical and physiological characteristics of brain structures, and having a history of mental illnesses other than AUD. All patients were diagnosed with AUD using the Turkish version of the Structured Clinical Interview for DSM-5 (SCID-5) (Elbir et al., 2019). Appointments for MRI were given to the participants who met the necessary criteria. The study initially included 17 healthy controls and 17 cases. However, two patients were subsequently excluded from the study because they were unable to tolerate the MRI procedures. Following the psychiatric interview, participants completed the sociodemographic data form, the Alcohol Use Disorders Identification Test (AUDIT), the Michigan Alcoholism Screening Test (MAST), and the Severity of Alcohol Dependence Questionnaire (SADQ-C) (Saunders et al., 1993; Selzer, 1971; Stockwell et al., 1983).

Magnetic Resonance Imaging Procedure

All imaging procedures were conducted using a 3.0 Tesla scanner, with participants positioned comfortably and their heads securely held in place (Philips Ingenia, Philips Medical Systems, Best, The Netherlands). At the end of the study period, volumetric

measurements of the MR images suitable for the study were made by the radiology department. Volume measurements were made manually with the help of the AW Server 3.2 Ext 3.0 program by painting the cross-sectional area of interest. While the T2 Flair sequence was used for VTA volume, T1-weighted images without fat suppression were used for other volume measurements. A three-dimensional fast field echo (FFE) T1-weighted dataset was used to scan the entire brain. T1-weighted images with 1 mm continuous sections were acquired in the axial, sagittal, and coronal planes. The following parameters were used to obtain brain imaging: echo time (TE) 3.8 ms, repeat time (TR) 8.2 ms, number of stimulus 1, field of view (FOV) 240 × 240 mm, rotation angle 8°, matrix size 512, and resolution 1 × 1 × 1 mm. Measurements were made by neuroradiologists blinded to the identity and diagnosis of the participants. Measurements were repeated bilaterally in ten selected subjects to determine within-rater reliability. In this procedure, the intraclass correlation coefficient for all regions was found to be above 0.87, which indicates sufficient reliability. Standard neuroanatomical atlases were used to trace and define the borders of the relevant regions (Desikan et al., 2006; Jackson & Duncan, 1996; Patel & Friedman, 1997; Yuh & Afifi, 1994). Figures 1 – 5 presents sections from the measurements.

Statistical Analysis

The Statistical Package for the Social Sciences, version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) was used to conduct the statistical analyses. The Shapiro – Wilk test was used to determine whether or not the data displayed a normal distribution. The chi-square test was used to compare categorical variables. Using the Student's *t*-test, continuous numerical data with a normal distribution were assessed. To lessen the impact of confounding variables in the measurement comparison, the ANCOVA test was employed. The Pearson Correlation Analysis Test was utilized to assess the correlation between volumes and scale scores.

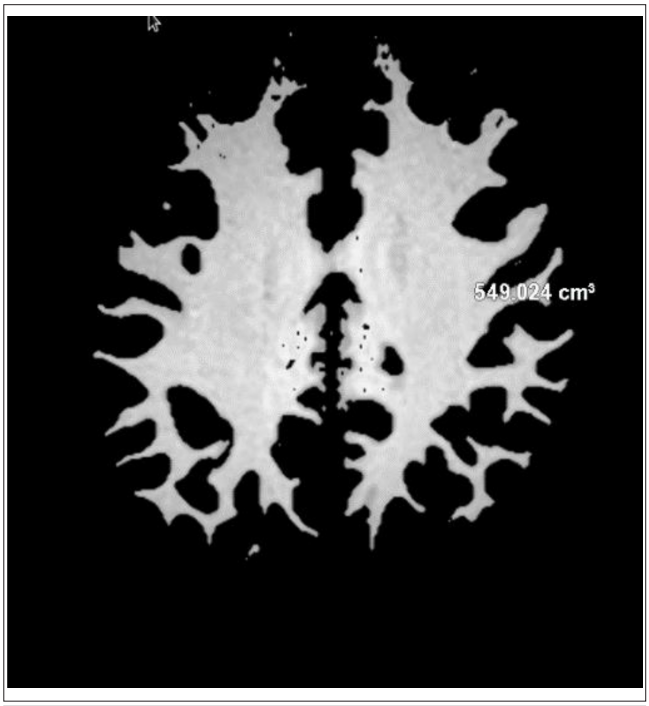

Figure 1. An Image of White Matter Volume Measurement.

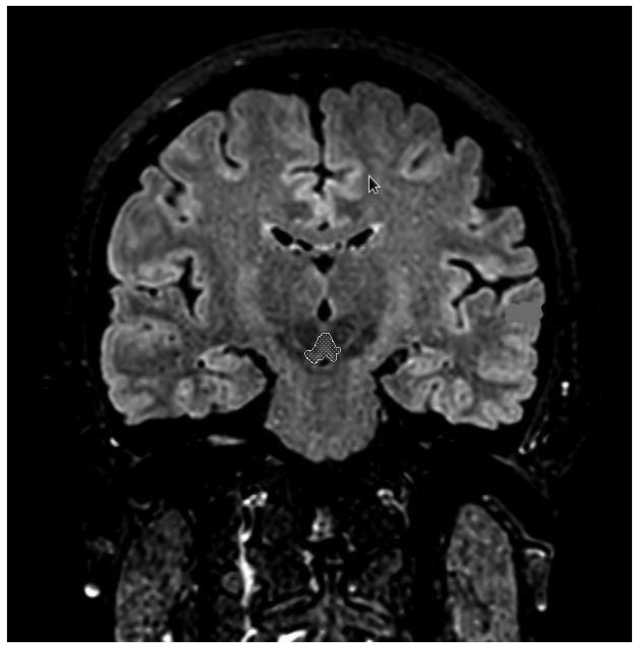

Figure 2. An Image of VTA Volume Measurement.

Results

The study included 17 individuals without any health problems as the control group and 15 individuals with AUD as the case group. The case group's mean age was 36.86 ± 11.03, while the control group's mean age was 29.05 ± 6.40 ($p < .05$). The sociodemographic data of the groups are summarized in Table 1.

The mean duration of alcohol consumption in the case group was 8.86 ± 3.13 (min = 5, max = 15) years. The mean amount of alcohol consumption was reported as 10.13 ± 4.59 beer (min = 5, max = 20). According to the scale scores and clinical evaluation, the severity of alcohol dependence in the case group was evaluated as moderate. The scale scores of the case group are summarized in Table 2. Scale scores were calculated as zero in the control group because there was no alcohol use, including social drinking.

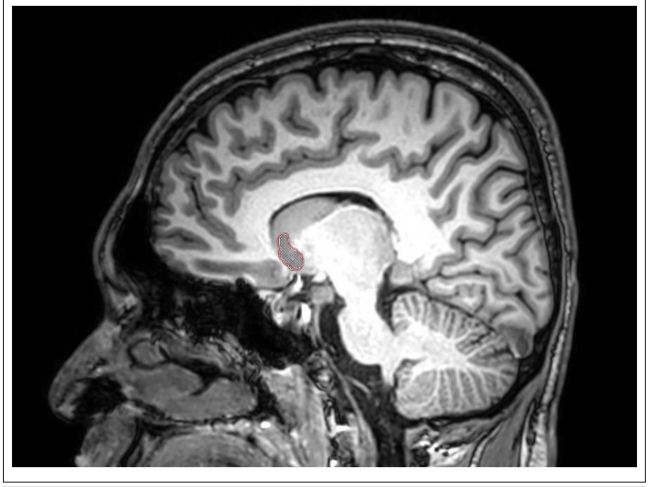

Figure 3. An Image of NAc Volume Measurement.

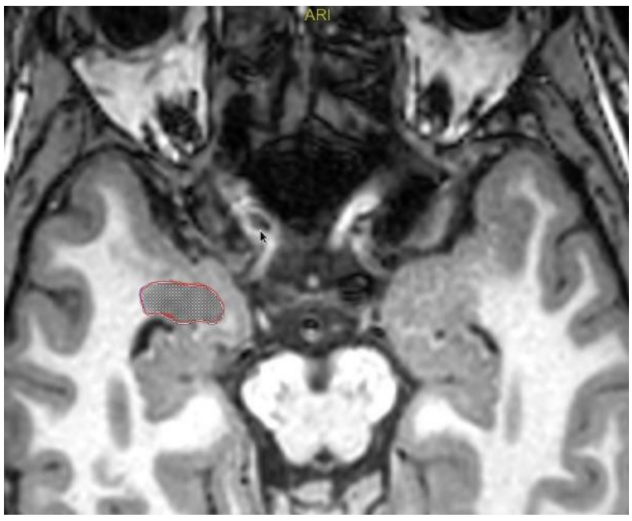

Figure 4. An Image of Amygdala Volume Measurement.

While the white matter volume of the control group was 616.17 ± 29.44 cm^3, this value was found to be 619.00 ± 45.98 cm^3 in the AUD group. Regarding white matter volumes, there was no statistically remarkable difference between the groups ($p > .05$). While the mean gray matter volume was 694.11 ± 44.13 cm^3 in the control group, it was 668.00 ± 66.78 cm^3 in the AUD group. The AUD group had a reduced gray matter volume; nonetheless, there was no statistically significant change ($p > .05$).

Ventral tegmental area volume was found to be 0.15 ± 0.01 cm^3 in both groups. The right NAc volume was 0.74 ± 0.14 cm^3 in the control group, while it was 0.72 ± 0.18 cm^3 in the AUD group. While the left NAc volume was 0.74 ± 0.16 cm^3 in the control group, it was 0.70 ± 0.14 cm3 in the AUD group. The two groups' VTA and NAc volumes did not significantly differ from one another ($p > .05$).

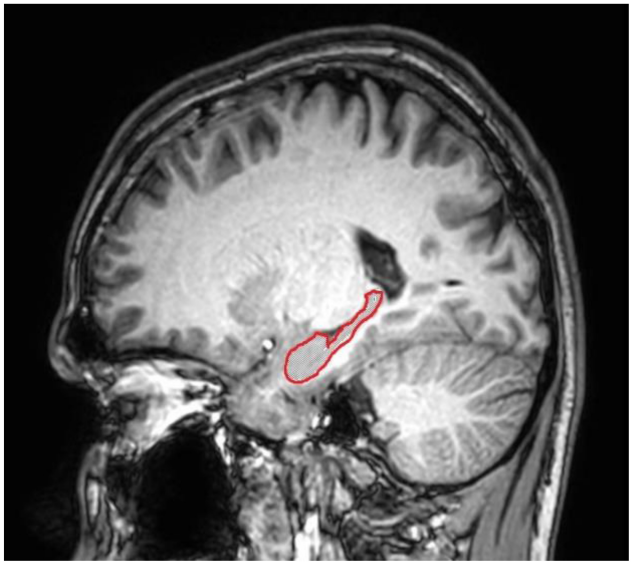

Figure 5. An Image of Hippocampus Volume Measurement. In this section, the red contour shows the boundaries of the hippocampus.

Table 1.
The Sociodemographic Data of the Groups

		Control (n = 17)	Case (n = 15)	
		***n* (%)**	***n* (%)**	***p***
Gender	Female	2 (11.8%)	1 (6.7%)	.548
	Male	15 (88.2%)	14 (93.3%)	
Marital status	Single	13 (76.5%)	6 (40%)	.036
	Married	4 (23.5%)	9 (60%)	
Handedness	Right	17	15	> .05
Working status	Working	7 (41.2%)	7 (46.7%)	.755
	Not working	10 (58.8%)	8 (53.3%)	
Tobacco use	Yes	0	15 (100%)	< .001
	No	17 (100%)	0	

Chi-square test was used.

While the volume of the right amygdala was 1.51 ± 0.26 cm^3 in the control group, it was 1.54 ± 0.41 cm^3 in the AUD group. The left amygdala volume was calculated as 1.55 ± 0.25 cm^3 in the control group, and it was found to be 1.51 ± 0.41 cm^3 in the AUD group. The amygdala volume was not substantially different between the groups ($p > .05$).

While the volume of the right hippocampus was 3.77 ± 0.52 cm^3 in the control group, it was 3.51 ± 0.36 cm^3 in the AUD group. The volume of the left hippocampus was 3.75 ± 0.45 cm^3 in the control group, while it was 3.52 ± 0.34 cm^3 in the AUD group. There was no statistically significant difference in the hippocampus volumes among the groups ($p > .05$). Comparison of volume measurements is summarized in Table 3.

Age and gender variables, which have been demonstrated in the literature to have an impact on volume measurements, were reevaluated using the ANCOVA test. Following the removal of the effects of gender and age from the analysis, there was a significant difference in the right hippocampus volume between the AUD and control groups ($F = 5.26$, $p = 0.03$). Apart from the right hippocampus volume, no other regions showed any appreciable variations between the two groups. The relationship between scale scores, volumetric measures, and the length and quantity of alcohol consumed was examined using Pearson correlation analysis. However, no statistically meaningful connection could be seen.

Discussion

To summarize the findings before starting the discussion, the main results of this study suggest that individuals with AUD

Table 2.
Mean Scale Scores of Case Group

	Case (n = 15) Mean ± SD
MAST	28.40 ± 12.51
SADQ-C	26.86 ± 14.83
AUDIT	23.93 ± 7.46

Student's *t*-test was used.
Note: MAST, Michigan Alcoholism Screening Test; SADQ-C, Severity of Alcohol Dependence Questionnaire.

show structural changes in the brain's reward system, specifically a significant reduction in the volume of the right hippocampus compared to healthy controls. No significant volumetric differences were found between the two groups in other brain regions studied, including the nucleus accumbens, VTA, and amygdala.

In AUD, significant changes in brain structure, particularly in total white and gray matter, highlight the disorder's profound impact on the brain. Chronic alcohol consumption is associated with widespread reductions in both gray and white matter volumes, which can contribute to the cognitive, emotional, and behavioral impairments seen in AUD (Asensio et al., 2016; Xiao et al., 2015; Yang et al., 2016). Gray matter loss is likely due to the neurotoxic effects of alcohol, including excitotoxicity, oxidative stress, and neuroinflammation (Seo et al., 2013). The loss in white matter integrity may be linked to disruptions in glial cell function and reduced myelination, further affecting neural communication (Monnig et al., 2013). The volume reductions in gray and white matter contribute to AUD's cognitive and behavioral symptoms, including memory impairment, reduced impulse control, and difficulties with problem-solving (Asensio et al., 2016). However, research also suggests that some degree of recovery in both gray and white matter volume can occur with sustained abstinence, underscoring the importance of early intervention and treatment (Bühler & Mann, 2011; Cardenas et al., 2007; Makris et al., 2008). In the present study, no significant difference was observed between the groups in terms of white and gray matter volumes. This may be explained by the fact that this group of patients has been undergoing detoxification and addiction treatment for some time (Monnig et al., 2013; Ruiz et al., 2013). As a second reason, there may be volume reductions in the regions of interest without a significant total volume reduction.

The hippocampus plays a crucial role in AUD, primarily due to its involvement in memory formation, emotional regulation, and decision-making processes. Chronic alcohol consumption is associated with structural and functional changes in the hippocampus, including reductions in its volume (Agartz et al., 1999; Mechtcheriakov et al., 2007). The hippocampus's vulnerability to alcohol's neurotoxic effects may result from its high concentration of glutamate receptors, which become overactive in the presence of excessive alcohol, leading to excitotoxicity and cell death (Mira et al., 2020). Additionally, alcohol disrupts neurogenesis in the hippocampus, further impairing its capacity to support cognitive flexibility and emotional processing (Shabani & Gharehziaaddin, 2021). The vast majority of studies in the literature indicate a reduction in hippocampal volume. Additionally, it has been documented that there is a substantial increase in volume following treatment (Demirakca et al., 2011; Zou et al., 2018). In the present study, while the volume of the left hippocampal region decreased to a level approaching significance in the AUD group, the right hippocampal volume decreased significantly when the effects of age and gender characteristics were taken out of the analysis.

The nucleus accumbens (NAc) plays a critical role in AUD due to its involvement in the brain's reward circuitry and the reinforcement of addictive behaviors. This region, a central component of the mesolimbic dopamine system, is highly sensitive to the dopamine release triggered by alcohol consumption, reinforcing the pleasurable effects of alcohol and driving craving and compulsive use. Functional MRI studies in individuals with AUD often show altered activity in the NAc in response to alcohol-related cues, indicating heightened sensitivity that may perpetuate the cycle of addiction. Structurally, MRI studies reveal that chronic alcohol use is associated with reduced volume in the NAc (Bracht et al., 2021; Sullivan et al., 2005). These structural changes likely reflect neurodegeneration from prolonged exposure to alcohol and are thought to contribute to the chronic relapsing nature of AUD (Makris et al., 2008). Thus, the NAc is not only pivotal in understanding the neurobiological mechanisms underpinning AUD but also serves as a potential target for therapeutic interventions aimed at modifying reward pathways. Contrary to the majority, some studies in the literature report that NAc volume does not decrease but increases (Sousa et al., 2020). The increased NAc volume may indicate a delay in typical neuromaturation processes, such as synaptic pruning, which normally reduce gray matter volume during adolescence. Alcohol use may disrupt these developmental trajectories, leading to increased or altered growth in certain brain areas. It has been shown that there is a volume increase in the NAc after treatment, as in the regions mentioned above. In this study, both right and left NAc volumes were found to be decreased in the alcoholic group, but this was not found to be statistically significant. The presence of conflicting results in the literature regarding NAc volume changes suggests the need for further studies with larger sample sizes.

The amygdala volume in individuals with AUD has been a subject of significant interest in neuroimaging research. Studies consistently indicate that AUD is associated with reductions in amygdala volume (Dager et al., 2015; Fein et al., 2006; Grace et al., 2021; Wrase et al., 2008). The amygdala, which plays a critical role in emotional processing, fear, and reward, may undergo structural changes as a result of chronic alcohol consumption (Wrase et al., 2008). These alterations are thought to reflect the neurotoxic effects of alcohol, which can impair neuroplasticity and promote the loss of gray matter. The reduced amygdala volume in AUD is often linked to emotional dysregulation and heightened anxiety, common features of the disorder (Sinha, 2022). Interestingly, some research suggests that these volume reductions may be partially reversible with sustained abstinence, indicating the potential for neuroplasticity and recovery (Wrase et al., 2008). However, the extent and speed of this recovery are still debated, and the relationship between amygdala volume and clinical outcomes remains complex. Additionally, individual factors such as the severity and duration of alcohol use, as well as genetic predispositions, may influence the degree of structural changes observed in the amygdala. Some studies have reported that the volume of the amygdala is small before AUD and that this increases susceptibility to AUD (Benegal et al., 2007; Dager et al., 2015).

The VTA plays a critical role in the brain's reward and motivation circuits, particularly through its dopaminergic projections to regions like the nucleus accumbens. In AUD, structural changes in the VTA are frequently reported, with studies showing reductions in VTA volume that likely contribute to altered dopamine signaling, leading to impaired reward processing (Beck et al., 2012; Bloomer et al., 2004). Chronic alcohol exposure can lead to neurotoxic effects in this region, affecting neuroplasticity and

potentially decreasing the number of dopamine-producing neurons. This reduction in dopaminergic output is thought to contribute to the decreased sensitivity to natural rewards and the increased sensitivity to alcohol-related cues seen in individuals with AUD, reinforcing the cycle of addiction and craving (Crews et al., 2015).

Some research suggests that structural changes in the VTA may also be linked to increased stress responsivity and mood dysregulation, given the role of the VTA in processing stress and emotional stimuli (Bouarab et al., 2019). Additionally, reductions in VTA volume might exacerbate the challenges of withdrawal and abstinence, as the region's compromised reward function may make it harder for individuals to experience pleasure or motivation from non-alcoholic sources (Makris et al., 2008). However, while VTA volume changes have been documented, more research is needed to clarify the timeline and degree of these alterations, especially with prolonged abstinence, as evidence on the reversibility of VTA structural changes in AUD remains mixed.

Limitations and Future Directions

Limitations of this study include a relatively small sample size, which may limit the generalizability of the findings. Another limitation involves the manual tracing method used for volumetric measurements, which may introduce variability and reduce the reproducibility of the results. Additionally, some participants in the study had been abstinent or receiving treatment for only a short period, which might have influenced the observed brain volumes. Longitudinal studies tracking structural changes over longer periods of abstinence or treatment are needed to clarify the reversibility of volumetric alterations in individuals with AUD. Future investigations could also explore more nuanced factors such as the duration and intensity of alcohol use, genetic predispositions, and co-occurring conditions to better understand the mechanisms underlying structural brain changes in AUD.

In conclusion, structural changes in the brain in patients with AUD. These changes may be directly or indirectly related to many clinical symptoms of addiction. Studies with larger samples are needed to directly correlate structural changes with clinical presentation.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: This study was approved by Ethics Committee of Firat University (Approval no: 2020/02-11; Date: 02/11/2020).

Informed Consent: Written informed consent was obtained from the patients/patient who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.F.T., M.A.; Design – M.F.T., M.A.; Supervision – M.G.G., H.Y., M.A.E.; Resources – H.Y., O.S., M.A.E.; Materials – H.Y., O.S., M.A.E.; Data Collection and/or Processing – M.F.T., M.A.E., M.G.G., M.A.E.; Analysis and/or Interpretation – M.F.T., M.A.; Literature Search – M.F.T., M.A., M.G.G., O.S.; Writing – M.F.T., M.A., M.G.G.; Critical Review – H.Y., O.S., M.A.E.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The research project was funded by FÜBAP (Firat University Scientific Research Projects Management Unit). Project No: TF.20.03.

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