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Research Article/Özgün Araştırma

Comparison of brain volume measurements in methamphetamine use disorder with healthy individuals using volbrain method

Metamfetamin kullanım bozukluğunda beyin hacmi ölçümlerinin volbrain yöntemi kullanılarak sağlıklı bireylerle karşılaştırılması

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Abstract

Aim: This study aims to examine brain structures in individuals with methamphetamine use disorder (MUD) and to understand the possible effects of methamphetamine on these structures.

Materials and Methods: The study was retrospectively evaluated in 21 MUD and 21 healthy controls. VolBrain segmentation method was used.

Results: Grey Matter (GM), Cortical GM, Cerebrum total, and GM volumes were found to be less and significantly higher in MUD compared to healthy controls (p<0.01). Accumbens, Basal Forebrain, Caudate, Pallidum, Putamen, and Parietal Lobe volumes were increased in MUD (p<0.01). Amygdala, Hippocampus, Ventral Diencephalone, Frontal Lobe, Posterior Orbital Gyrus, Precentral Gyrus, Temporal Lobe, Calcarine Cortex, Middle Occipital Gyrus, Superior Occipital Gyrus, Limbic Cortex volumes were significantly smaller in MUD compared to healthy controls.

Conclusion: This study helped us better understand MUD's effects on brain structures. It also provided important information for developing effective strategies for treating and preventing MUD.

Keywords: Methamphetamine; Brain; Grey matter; Basal forebrain.

Öz

Amaç: Bu çalışmanın amacı, metamfetamin kullanım bozukluğu (MKB) olan bireylerde beyin yapılarını incelemek ve metamfetaminin bu yapılar üzerindeki olası etkilerini anlamaktır.

Gereç ve Yöntem: Çalışmada 21 MKB ve 21 sağlıklı kontrol retrospektif olarak değerlendirildi. VolBrain segmentasyon yöntemi kullanıldı.

Bulgular: Substantia grisea (SG), kortikal SG serebrum total ve SG hacimleri sağlıklı kontrol grubuna kıyasla daha az ve anlamlı bulunmuştur (p<0,01). Accumbens, pars basalis telencephali, lobus caudatus, globus pallidus, putamen ve lobus parietalis hacimleri MKB'de artmıştır (p<0,01). Amygdala, hippocampus, ventral diensefalon, lobus frontalis, gyrus orbitalis posterior, gyrus precentralis, lobus temporalis, calcarine cortex, gyrus occipitalis medium, gyrus occipitalis superior, lobus limbicus hacimleri MKB'de sağlıklı kontrollere kıyasla anlamlı derecede küçüktü.

Sonuç: Bu çalışma, MKB'nin beyin yapıları üzerindeki etkilerini daha iyi anlamamıza yardımcı oldu. Ayrıca, MKB tedavisi ve önlenmesi için etkili stratejiler geliştirmek için önemli bilgiler sağlamıştır.

Anahtar Kelimeler: Metamfetamin; Beyin; Gri madde; Bazal ön beyin.

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Introduction

Methamphetamine crystal (chalk or ice) is an addictive stimulant that can be administered orally, smoked, snorted, or injected. Smoking or intravenous injection rapidly delivers methamphetamine to the brain, resulting in a sudden and intense euphoria. Methamphetamine use is associated with serious neurological and physical consequences and has become a severe public health problem worldwide[1]. Methamphetamine was discovered in Japan in 1919 and commercialized in 1938 under Pervitin. It was trendy for tired night shift workers and was used by Germany during World War II to treat fatigue in weary army troops. Methamphetamine became widely used in 1943 to treat various disorders, including narcolepsy, depression, obesity, alcoholism, and attention deficit hyperactivity disorder[2]. The euphoric effects of methamphetamine occur due to the release of the neurotransmitter dopamine, which is involved in the experience of pleasure, motivation, and motor function. However, long-term use of methamphetamine causes molecular changes in the dopamine system, contributing to nerve terminal brain damage and impaired motor skills, rapid cognitive decline, increased anxiety, psychotic disorders, violent behavior, hallucinations, delusions, and depression[3,4]. Although drugs of abuse have been shown to alter brain structures over time, there is limited information about how methamphetamine use may affect the brain over time[5]. The existing literature on this matter needs more unequivocal clarity. Within this context, individuals who use methamphetamine exhibit an array of neuroanatomical differences compared to non-users and control participants[6-8]. However, the specific brain regions involved in these disparities vary among studies. While some investigations have reported reduced cortical volumes in methamphetamine users[9,10], other studies have findings, including increased volumes in distinct brain regions such as the basal ganglia and parietal lobe[11].

Moreover, another finding was that methamphetamine use was more common in the male gender[6]. These results within the existing literature underscore the complexity of the impact of methamphetamine use on brain morphology, and they emphasize the need for further research to delineate the precise mechanisms and factors contributing to these observed differences. In addition, a more comprehensive understanding of the neuroanatomical changes associated with methamphetamine use is essential for physicians and nurses, who have active roles in this field, to determine effective prevention and treatment strategies for substance abuse.

To the best of our knowledge, this is the first study in which 238 different brain segments of each participant were measured with the volbrain method in methamphetamine use disorder (MUD). The aim of this study was to obtain information about the course of the disease in individuals diagnosed with MUD and to determine the extent to which the volumes of the brain and other structures related to the disease are affected.

Materials and Methods

Type of the study

This study is cross-sectional and retrospective.

The sample size of the study

This study evaluated 21 male patients who were admitted to the hospital due to MUD, diagnosed with MUD in urinalysis, had no serious systemic disease, did not use alcohol, and was followed up in Atatürk University Psychiatry Clinic. Healthy controls consisted of 21 male participants who were compatible with the patient group among individuals without any health problems[12,13] registered in Atatürk University Archives and were evaluated retrospectively.

Data collection tools

MR protocol: The MR protocol used in the study was as follows. High-resolution T1-weighted 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) images were used to show the anatomical structure. Sequence=Sagittal, Repeat time=1900 ms/2.84s, Flip angle=15o, Echo time=2.67 ms, FOV=256 mm2, Matrix=256x256, Number of

slices=160, Slice thickness=1 mm, Resolution=1x1x1x1 mm3 isotropic.

VolBrain Method: VolBrain (https://volbrain.net/) is an open access platform for automatic segmentation of various brain structures[14-16]. We used the segmentation method with default VolBrain T1w volume metric images and performed total cerebrum volumetric analysis in the study groups. The Mricloud method is a web-based software developed by Johns Hopkins University. It is used for volume calculation with brain parcellation in MR images. In order to perform volume calculation with VolBrain, MR images must be converted to "gz or rar" format. The process steps to be performed for these calculations are as follows.

A file with the extension "DICOMDIR" is opened through a DICOM viewer software program. To show the anatomical structure, high-resolution T1-weighted 3D MPRAGE images are opened with mricron, and a file with gz extension in compressed FSL format is created. In the next step, the images converted to "gz" format of the exported images are uploaded to the volbrain web page. Registration is done. Gz extension files are uploaded to the system. In approximately 5-10 minutes, the volumes of all regions in the brain are obtained. The results are saved as pdf. Again, images are recorded as native and mni, and a three-dimensional evaluation is made visually with itksnap.[14,15]

In this study, the AssemblyNet partition was selected from VolBrain measurements. AssemblyNet is a large central nervous system ensemble for 3D whole-brain MRI segmentation[16]. Volumetric values of all parts of the brain were measured in cm3 and percentages, and total-right-left ratios were measured. A total of 462 different data were obtained from each participant. white matter (WM), grey matter (GM), subcortical GM, cortical GM, cerebellar GM, cerebro spinal fluid (CSF), brain (WM+GM), intracranial cavity (IC), cerebrum, cerebrum WM, cerebrum GM, cerebellum, cerebellum WM, cerebellum GM, vermis, brainstem were measured. Subcortical structures accumbens, amygdala, basal forebrain, caudate, hippocampus, pallidum, putamen, thalamus, and ventral diencephalon were measured. Among the cortical structures, frontal lobe and frontal lobe parts, the frontal pole, gyrus rectus, opercular inferior frontal gyrus, orbital inferior frontal gyrus, triangular inferior frontal gyrus, medial frontal cortex, middle frontal gyrus, anterior orbital gyrus, lateral orbital gyrus, medial orbital gyrus, posterior orbital gyrus, precentral gyrus, precentral gyrus medial segment, subcallosal area, superior frontal gyrus, superior frontal gyrus medial segment, supplementary motor cortex were measured. Temporal lobe and fusiform gyrus, planum polare, planum temporale, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, transverse temporal gyrus, and temporal pole were measured. The parietal lobe and angular gyrus, postcentral gyrus, postcentral gyrus medial segment, precuneus, superior parietal lobule, and supramarginal gyrus were measured. The occipital lobe and calcarine cortex, cuneus, lingual gyrus, occipital fusiform gyrus, inferior occipital gyrus, middle occipital gyrus, superior occipital gyrus, and occipital pole were measured. The limbic cortex and entorhinal area, anterior cingulate gyrus, middle cingulate gyrus, posterior cingulate gyrus, and parahippocampal gyrus were measured. The insular and insular cortex parts, anterior insula, posterior insula, central operculum, frontal operculum, and parietal operculum were measured. CSF, inferior lateral ventricle, lateral ventricle, third ventricle, fourth ventricle, and external CSF were measured (Figure 1).

Data analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corporation, Armonk, New York, USA). The priori power analysis was performed using the G-Power 3.1.9.4 program to determine that the sample size was sufficient, the effect size was 1.1, and the power was 0.90 at the 95% confidence interval, at a significance level of 0.05[13]. These values indicate that the sample size is at the desired level. Values were presented as mean and standard deviation. Mann-Whitney U test was used to evaluate

differences between groups. $p<0.05$ was considered statistically significant.

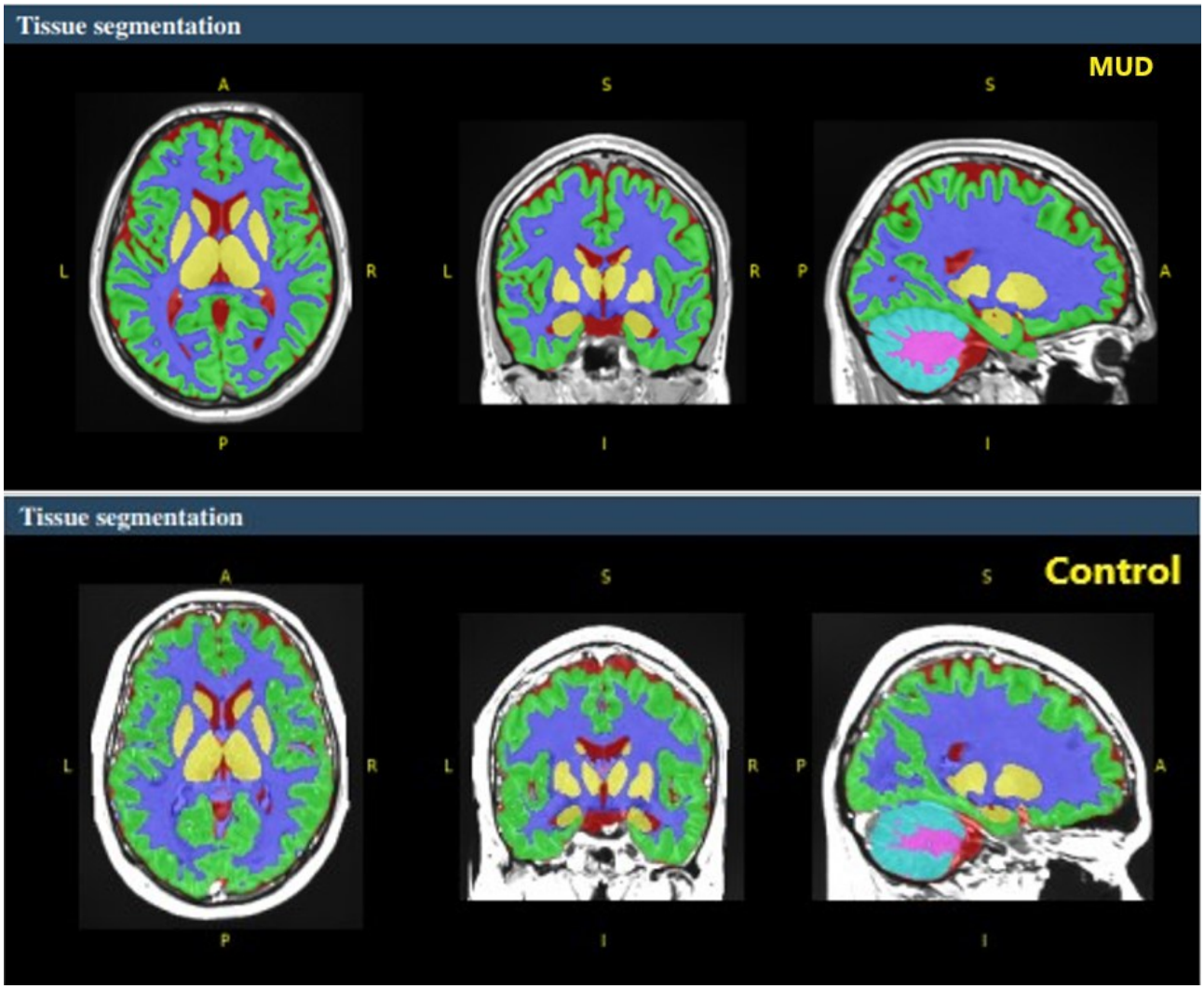

Figure 1. The top image shows brain volume measurements in individuals with methamphetamine use disorder, and the bottom image shows brain volume measurements in healthy controls.

Ethics committee approval

Ataturk University Faculty of Medicine Clinical Research Ethics Committee with the ethics committee decision numbered B.30.2.ATA.0.01.00/128 and dated 26.01.2023. This study conformed to the Helsinki Declaration.

Results

Since all MUD in the study were male, the control group was also selected from male healthy individuals. The mean age of MUD was 40.14±6.82 years, and the mean age of the control group was 41.33±5.0 years (p=0.33). The body mass index was 22.03±2.03 in MUD and 22.66±1.65 in the control group (p=0.48).

The volumes of WM, GM, subcortical GM, cortical GM, cerebellar GM, WM+GM, IC, cerebrum total, cerebrum WM, and cerebrum GM were decreased in MUD compared to healthy controls. In addition, it was found that GM, cortical GM, WM+GM, IC, cerebrum total, cerebrum total, and cerebrum total GM volumes decreased statistically significantly in MUD (Table 1). In MUD, the volume measurements of the total, right, and left parts of the cerebellum, cerebellum WM, cerebellum GM, vermis, and brainstem sections were less than in healthy individuals. However, no statistically significant difference was found. In addition, accumbens volume increased in MUD, while hippocampus, thalamus and ventral diencephalon volumes decreased in healthy controls. In addition, statistically significant differences were found in the accumbens, hippocampus, and ventral diencephalon volume measurements of MUD

and healthy individuals (Table 1). Amygdala, one of the subcortical structures, decreased in MUD, while basal forebrain, caudate, pallidum, and putamen volume measurements increased significantly (Table 2). In addition, the frontal lobe, temporal lobe, occipital lobe, limbic cortex, and insular cortex volume measurements were significantly reduced in MUD. Parietal lobe volume increased, but no statistically significant difference was found (Table 2, Table 3). In MUD, inferior lateral ventricle, lateral ventricle, third ventricle, and fourth ventricle volume measurements from CSF sections were measured less, and it was found that the third ventricle volume measurement was statistically significantly decreased compared to healthy individuals (Figure 2).

Table 1. Comparison of brain volume (Cerebrum, cerebellum, vermis, brainstem, accumbens hippocampus. Thalamus and ventral diencephalon) measurements in methamphetamine use disorder and healthy individuals.

	Methamphetamine Mean±SD	**Control Mean±SD**	***p***
White Matter cm^3	450.83±58.70	523.12±165.35	0.308
Grey Matter cm^3	643.96±117.14	749.52±71.872	**0.004****
Subcortical cm^3	29.94-15.81	34.18±12.85	0.296
Cortical GM cm^3	512.61±94.13	608.80±72.31	**0.004****
Cerebellar GM cm^3	101.88±15.50	106.53±19.48	0.458
Cerebro Spinal Fluid cm^3	216.01±98.75	208.39±146.51	0.372
Brain (WM+GM) cm^3	1094.81±141.58	1272.65±203.13	**0.006****
Intracranial Cavity cm^3	1325.28±142.79	1495.87±323.69	**0.051**
Cerebrum total cm^3	973.18±123.71	1141.24±201.18	**0.004****
Cerebrum right cm^3	515.60±61.67	572.75±102.271	0.128
Cerebrum left cm^3	457.57±103.14	568.46±100.79	**0.009****
Cerebrum total WM cm^3	430.63±59.33	481.62±193.91	0.678
Cerebrum right WM cm^3	232.01±42.54	250.37±87.54	0.811
Cerebrum left WM cm^3	198.61±47.91	247.83±79.84	0.064
Cerebrum total GM cm^3	542.55±105.55	642.98±70.17	**0.005****
Cerebrum right GM cm^3	283.58±65.01	322.33±31.98	0.110
Cerebrum leftt GM cm^3	258.96±63.76	320.65±42.77	**0.004****
Cerebellum total cm^3	111.35±19.29	120.30±18.01	0.162
Cerebellum right cm^3	58.44±10.64	63.75±10.19	0.178
Cerebellum left cm^3	52.91±13.17	56.55±10.51	0.345
Cerebellum WM total cm^3	20.20±9.08	24.86±4.77	0.128
Cerebellum WM right cm^3	10.70±4.80	12.79±2.79	0.421
Cerebellum WM left cm^3	9.51±5.64	12.07±2.24	0.263
Cerebellum GM total cm^3	91.14±12.51	95.44±18.35	0.489
Cerebellum GM right cm^3	47.73±6.73	50.96±11.35	0.513
Cerebellum GM left cm^3	43.41±9.31	44.47±9.51	0.930
Vermis cm^3	10.27±3.22	11.09±2.04	0.588
Brainstem cm^3	14.48±5.18	14.83±4.37	0.772
Accumbens total cm^3	0.84±0.12	0.35±0.32	**0.001****
Accumbens right cm^3	0.38±0.07	0.18±0.15	**0.001****
Accumbens left cm^3	0.45±0.06	0.21±0.19	**0.001****
Hippocampus total cm^3	3.70±2.82	6.78±1.62	**0.001****
Hippocampus right cm^3	2.04±1.41	3.40±0.78	**0.001****
Hippocampus left cm^3	1.65±1.52	3.37±0.90	**0.001****
Thalamus total cm3	12.32±5.24	14.16±3.29	0.443
Thalamus right cm3	6.57±2.91	7.25±1.17	0.489
Thalamus left cm3	5.74±3.09	6.91±2.16	0.273
Ventral Diencephalon total cm3	7.38±3.59	9.72±3.15	**0.044***
Ventral Diencephalon right cm3	3.83±1.85	5.24±2.11	0.222
Ventral Diencephalon left cm3	3.55±1.91	4.71±1.46	**0.048***

SD: Standard Deviation, WM: White Matter, GM: Grey Matter. **: $p<0.01$, *: $p<0.05$, Mann Whitney U Test was used.

Table 2. Comparison of volume measurements of amygdala, basal forebrain, caudate, pallidum and putamen from subcortical structures, limbic cortex and ınsular cortex in methamphetamine use disorder and healthy ındividual.

	Methamphetamine Mean±SD	Control Mean±SD	*p*
Amygdala total cm3	0.76±0.74	1.94±0.47	**0.001****
Amygdala right cm3	0.41±0.40	0.98±0.23	**0.001****
Amygdala left cm3	0.34±0.36	0.94±0.24	**0.001****
Basal forebrain total cm^3	0.56±0.18	0.36±0.21	**0.003****
Basal forebrain right cm^3	0.26±0.08	0.17±0.11	**0.019***
Basal forebrain left cm^3	0.31±0.11	0.18±0.12	**0.002****
Caudate total cm^3	4.92±1.84	3.11±2.71	**0.016***
Caudate right cm^3	2.55±0.86	1.49±1.26	**0.005****
Caudate left cm^3	2.36±1.06	1.61±1.47	**0.054***
Pallidum total cm^3	2.39±0.76	1.27±1.11	**0.004****
Pallidum right cm^3	1.31±0.31	0.66±0.55	**0.001****
Pallidum left cm^3	1.08±0.54	0.62±0.56	**0.039***
Putamen total cm^3	7.02±2.24	4.56±2.86	**0.005****
Putamen right cm^3	3.93±0.71	2.41±1.48	**0.001****
Putamen left cm^3	3.08±1.71	2.16±1.43	**0.054***
Limbic cortex	34.70±11.33	45.05±5.97	**0.003****
Entorhinal area	2.99±1.43	3.47±1.51	0.273
Anterior cingulate gyrus	9.16±4.28	10.79±3.03	0.059
Middle cingulate gyrus	7.55±2.95	11.29±1.82	**0.001****
Posterior cingulate gyrus	8.83±3.73	13.24±6.92	0.07
Parahippocampal gyrus	6.16±1.50	6.20±2.58	0.263
Insular cortex	20.93±11.56	25.39±11.78	0.385
Anterior insula	6.10±3.27	7.49±3.05	0.358
Posterior insula	3.14±1.77	3.94±1.82	0.089
Central operculum	5.95±2.86	7.68±2.63	**0.038***
Frontal operculum	2.59±1.70	3.35±1.54	0.178
Parietal operculum	3.14±2.21	3.93±2.01	0.182

SD: Standard Deviation, **: $p<0.01$, *: $p<0.05$, Mann Whitney U Test was used.

Table 3. Comparison of volume measurements of frontal lobe, temporal lobe, occipital lobe, limbic cortex, and insular cortex in methamphetamine use disorder and healthy individuals.

Cortical	Methamphetamine Mean±SD	Control Mean±SD	*p*
Frontal lobe	164.24±32.415	188.63±51.31	**0.017***
Frontal pole	6.60±1.62	89.62±26.81	0.076
Gyrus rectus	2.65±1.94	3.30±1.72	0.473
Opercular inf. frontal gyrus	5.24±2.24	6.21±2.29	0.186
Orbital inf. frontal gyrus	2.24±0.97	3.24±0.90	**0.002****
Triangular inf. frontal gyrus	6.52±1.77	7.95±2.06	**0.043***
Medial frontal cortex	2.27±1.63	3.28±1.41	**0.036***
Middle frontal gyrus	35.25±7.32	45.29±16.91	**0.031***
Anterior orbital gyrus	3.33±0.98	3.53±1.50	0.606
Lateral orbital gyrus	3.86±1.38	4.27±1.56	0.505
Medial orbital gyrus	6.75±2.62	8.18±1.55	0.151
Posterior orbital gyrus	5.46±1.81	7.96±2.21	**0.001****
Precentral gyrus	24.01±5.82	28.23±3.12	**0.021***
Precentral gyrus medial seg.	4.47±2.49	5.96±1.11	0.148
Subcallosal area	1.80±0.79	2.32±0.75	**0.043***
Sup. frontal gyrus	30.47±4.92	36.04±11.41	0.162
Sup. frontal gyrus medial seg.	12.93±5.12	13.10±3.67	0.85
Supplementary motor cortex	10.13±3.87	12.32±1.30	**0.036***
Temporal lobe	103.67±18.51	116.69±13.44	**0.033***
Fusiform gyrus	13.41±4.38	16.05±2.81	0.186
Planum polare	2.85±1.45	3.93±1.88	**0.017***
Planum temporale	2.47±1.70	3.26±1.89	0.186
Inf. temporal gyrus	24.22±3.38	23.21±4.87	0.473
Middle temporal gyrus	28.60±9.71	33.23±4.08	**0.011***
Sup. temporal gyrus	13.24±3.97	16.12±2.29	**0.02***
Transverse temporal gyrus	2.12±1.42	2.43±1.30	0.458

Temporal pole	16.73±4.14	18.42±3.41	0.213
Parietal lobe	117.78±35.49	115.08±17.27	0.93
Angular gyrus	27.64±15.58	25.04±4.60	0.99
Postcentral gyrus	19.82±5.07	23.49±5.62	**0.024***
Postcentral gyrus medial seg.	1.64±0.86	1.77±0.86	0.562
Precuneus	24.36±8.28	22.14±7.03	0.371
Sup. parietal lobule	28.26±9.63	24.17±3.73	0.057
Supramarginal gyrus	16.04±4.43	17.99±3.53	0.195
Occipital lobe	77.65±13.07	84.55±17.51	0.213
Calcarine cortex	5.42±2.80	7.11±2.54	**0.038***
Cuneus	7.34±4.09	9.03±3.63	0.195
Lingual gyrus	17.02±6.27	16.54±5.19	0.473
Occipital fusiform gyrus	8.77±1.64	9.32±1.76	0.358
Inf. occipital gyrus	14.83±4.25	16.09±5.24	0.372
Middle occipital gyrus	10.27±2.48	11.86±2.57	**0.005****
Sup. occipital gyrus	8.64±1.73	10.05±2.01	**0.011***
Occipital pole	4.96±1.72	5.00±2.49	0.93

SD: Standard Deviation, **: $p<0.01$, *: $p<0.05$, Mann Whitney U Test was used.

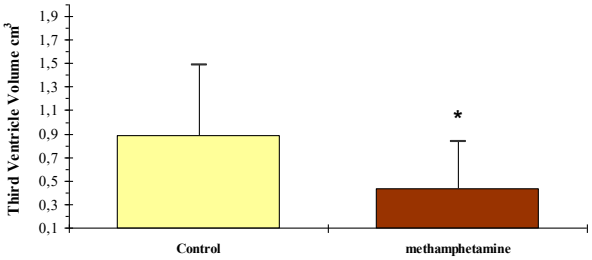

Figure 2. Third ventricle volume values (cm^3) *p=0.022.

Discussion

Substance use disorder is an increasing problem in our country and the world[17]. Methamphetamine, a potent sympathomimetic substance, shows its stimulant effect by causing the release of dopamine and norepinephrine from dopaminergic and noradrenergic nerve endings. Methamphetamine is more dangerous than other stimulants due to its acute complications, long-term neurotoxicity, and high addictive potential. In addition to being addictive, Methamphetamine causes many complications. These include epilepsy, vasculitis, severe headache, hypertension, tachycardia, hyperthermia, increased respiratory rate, and hemorrhagic and ischemic stroke, the most important of which may cause permanent damage to the central nervous system[18]. For this reason, studies on methamphetamine have always remained up-to-date in the literature[19,20]. In the studies on methamphetamine, some of the brain areas have been evaluated, and affected areas have been reported, but not all brain structures have been examined as a whole. In this study, 238 different regions of the brain in MUD and healthy controls were analyzed with the volbrain method, making it one of the first studies. Our study aimed to shed light on the potential changes in brain structure associated with methamphetamine consumption.

One of the most striking findings in studies on is the significant decrease in GM volume in methamphetamine users. It has been suggested that methamphetamine use may lead to structural changes in the brain, especially in decision-making, emotion regulation, and cognitive control[5,21-23] In this study, similar to the literature, decreases in GM volume were found in the measurements performed on MUD. The observed decrease in GM volume may reflect neuron loss and changes in neuron density due to the neurotoxic effects of methamphetamine. Cortical GM, also known as the cerebral cortex, is rich in cell bodies, dendrites, and synapses and plays a vital role in various cognitive, sensory, and motor functions in the brain. Methamphetamine disrupts the delicate balance of neurotransmitters in individuals and triggers neurotoxic effects[24,25]. Prior investigations in the field have consistently reported a notable decline in GM volume among individuals afflicted with MUD[6,24]. In this study, aligning with this existing body of literature, yielded compelling evidence of significantly diminished cortical GM volume, as well as reduced total GM volume within the cerebrum, in individuals diagnosed with MUD. The observed reduction in GM volume can be attributed to several factors, including neuron

loss and alterations in neuron density resulting from the neurotoxic effects of methamphetamine. These structural changes in the cerebral cortex, a dense region with cell bodies, dendrites and synapses, have a profound effect on cognitive, sensory and motor functions in the brain. The disruption of the intricate equilibrium of neurotransmitters induced by methamphetamine usage plays a pivotal role in triggering these neurotoxic effects. Such structural changes in GM may lead to a range of debilitating consequences for affected individuals. Specifically, the documented GM reduction is associated with cognitive deficits, impaired emotional regulation, and compromised executive functions. These impairments collectively underscore the complexity of the challenges faced by individuals grappling with MUD and emphasize the pressing need for comprehensive interventions and targeted treatments to address these profound structural alterations within the brain[24].

Located behind the bulbus and pons, below the tentorium cerebelli, the cerebellum is the most significant part of the rhombencephalon. The cerebellum is a compactly organized structure with many functions: movement, emotional memory, planning, and perception. In the literature, it has been reported that the cerebellum volume decreased in MUD[25-27]. In our study, cerebellum total, cerebellum WM, and cerebellum GM volumes were measured less in MUD. However, it was not statistically significant.

The accumbens is a crucial brain region that mediates various behaviors, including reward and satisfaction. Jernigan et al[11]. conducted a study in which they observed the impact of methamphetamine use on the nucleus accumbens, explicitly focusing on alterations in dopamine release and the volume of this brain region. Their findings revealed that methamphetamine use led to a significant increase in the volume of the nucleus accumbens.

In this study, the researchers assessed the volume of the nucleus accumbens in three specific dimensions: right, left, and total volumes. Their results demonstrated statistically significant increases in the volumes of the right, left, and total nucleus accumbens in individuals with MUD. These findings shed light on the neurobiological changes associated with chronic methamphetamine use, highlighting the profound impact of this substance on the structure and function of the nucleus accumbens, a vital component of the brain's reward system.

The hippocampus which has a role in the limbic system, memory, and especially short-term memory, is known to undergo hippocampal neurodegeneration in methamphetamine exposure[28]. Thompson et al[12] reported that the hippocampus volumes of MUD were 7.8% smaller than healthy subjects. Warton et al[29] found that methamphetamine exposure in the prenatal period was associated with decreased thalamus volume. Similarly, the hippocampus volume was smaller in this study compared to healthy subjects. The thalamus, one of the parts of the diencephalon, was also among the affected parts in MUD. The thalamus, an intermediate station for all sensory stimuli except odor, was volumetrically less in MUD[24]. In this study, the volume of the diencephalon and thalamus was also found to be less in MUD.

The amygdala, one of the subcortical structures, is responsible for controlling emotions, especially fear, and is involved in the formation and storage of memory related to emotional events and activation of the nervous system. Orikabe et al[30] found significant volume reductions in both amygdala and hippocampus in MUD compared to healthy controls. The degree of volume reduction was significantly greater in the amygdala than in the hippocampus. In the present study, amygdala volumes were significantly reduced in MUD.

The basal forebrain, caudate, pallidum, and putamen control many different functions, such as body movement planning, eye movements, and cognitive and emotional functions. These structures have been extensively investigated in studies on addiction. Jan et al[31] found increased putamen volume in MUD. Roos et al[32] found increased putamen volume in children prenatally exposed to methamphetamine. Lin et al[33]

reported that diffusion indices increased in the basal forebrain regions of methamphetamine users but emphasized that this increase was not significant. Berman et al[24] conducted a detailed study on methamphetamine users, reporting that pallidum, putamen, and caudate volumes increased in MUD. In this study, basal forebrain, caudate, pallidum, and putamen volumes were significantly increased in MUD compared to healthy controls.

Studies investigating individuals with MUD have consistently reported significant alterations in cortical brain volumes. Specifically, these investigations have highlighted volumetric changes within distinct cortical regions. For instance, Jia et al[4] documented a reduction in the volume of the Frontal Lobe in individuals with MUD. In concurrence with these findings, Aoki et al[34], Bartzokis et al[35] reported not only decreased Frontal Lobe volumes but also reduced volumes in the Temporal Lobe among MUD-afflicted individuals. Furthermore, Thompson et al[12] observed a diminished volume within the Limbic cortex, further emphasizing the widespread impact of methamphetamine on cortical brain regions. Interestingly, in the literature, there are studies by Jernigan et al[11] reporting an increase in parietal lobe volume in individuals with MUD, as well as studies reporting a decrease in parietal lobe volume[9]. This discrepancy underscores the complexity of structural alterations within the brain in response to methamphetamine use. In our study, we sought to contribute to this body of knowledge by investigating a broad spectrum of cortical regions, in line with the existing literature. Our findings align with prior research in detecting reduced volumes in several cortical regions, namely the Frontal Lobe, Temporal Lobe, Occipital Lobe, Limbic cortex, and Insular cortex among individuals with MUD. This concordance with previous research underscores the consistent nature of cortical volume reduction in MUD. Remarkably, our study also revealed an increase in Parietal lobe volume in individuals with MUD. This unique observation highlights the complexity of the impact of methamphetamine on cortical regions and further emphasizes the need for comprehensive investigations to elucidate the intricacies of structural changes within the brain in response to methamphetamine use.

Limitations

The limitation of this study is that the sample consisted only of male participants. This is due to the lack of female patients in the study's institution. Having only male participants prevented comparison between genders. The strength of our study is that it has significant strength in that it comprehensively examined the effects of MUD on brain structures, including 238 different brain regions. This provides a broader perspective and helps us understand which areas are particularly affected.

Conclusion

In conclusion, findings from studies on individuals with MUD reveal significant structural changes in the brain. MUD is associated with significant changes in the brain, including a decrease in cortical GM. Prolonged and excessive use of methamphetamine disrupts the delicate balance of neurotransmitters and triggers neurotoxic effects in the cortex. This vital region of the brain, responsible for decision-making, impulse control, and judgment, experiences a significant decrease in GM volume. As volume reduction occurs in the frontal lobe, temporal lobe, occipital lobe, limbic cortex, and insular cortex, cognitive deficits, emotional dysregulation, and impaired executive function can occur in individuals struggling with MUD. Understanding these structural changes is crucial not only to explain the mechanisms underlying MUD but also to inform targeted interventions and treatment strategies. The complex interplay between affected brain regions highlights the complexity of MUD and underscores the importance of addressing it as a multifaceted public health problem. Further research is needed to explore these structural changes' functional implications and develop comprehensive approaches to preventing and rehabilitating MUD.

Ethics Committee Approval

Ataturk University Faculty of Medicine Clinical Research Ethics Committee with the ethics committee decision numbered B.30.2.ATA.0.01.00/128 and dated 26.01.2023. This study conformed to the Helsinki Declaration.

Author Contributions

Study concept/design, data collecting: HÖ., GD., data analysis and interpretation GD. NA. NK, literature review, writers: GD., NA, NK, The final version of this article was read and approved by all authors.

Conflict of Interest

There is no conflict of interest to declare.

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