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Original Research

Corpus Callosum Atrophy in Alcohol-Dependent Men with Memory Disorders and Visual Attention Difficulties

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Abstract

Background: The earlier research confirm the relationship between structural changes in the corpus callosum and difficulties in attention and memory in the group of patients with alcohol use disorder (AUD). Nevertheless, the image of auditory and visual memory disorders in men with gradual atrophy of the corpus callosum and different alcohol abuse duration, it has not been explained yet. The overriding objective of this study was: (1) to determine whether there are principal and interaction effects of visuospatial and auditory-verbal memory on alcohol consumption and cross-sectional corpus callosum area in men with alcohol use disorder, (2) to assess the impact of callosal changes on the memory and visual attention processes. **Methods**: 97 men with alcohol use disorder were examined. T1-weighted scans were used to carry out corpus callosum segmentation and volumetric measurements. The cognition profile included two domains: attention, memory (visuospatial and auditory-verbal). **Results**: The results showed that participants with visuospatial memory disorder had inferior education background, and were characterized by a longer duration of alcohol abuse, more severe alcohol use disorder, and greater alcohol consumption per day. Second, alcohol-dependent men with auditory and visual memory disorders had a smaller frontal and posterior part of the corpus callosum areas. Additionally, among the alcohol-dependent men with memory disorders the smaller rostral body of corpus callosum was determined by the longer alcohol abuse duration. On the other hand, the smaller rostral body of corpus callosum was predicted by the older age only in alcohol-dependent men with normal memory. Among all examined individuals were observed a statistically significant relationships among visual attention, visuospatial memory and corpus callosum subregions including in particular genu and isthmus. **Conclusions**: The smaller corpus callosum cross-sectional area significantly affects visual attention and memory difficulties in alcohol use disorder, especially have differentiated the patients with normal and disordered memory. Longer alcohol abuse duration plays also a significant role in the corpus callosum atrophy in alcohol-dependent men with disordered memory (visuospatial in particular).

Keywords: alcohol use disorder (AUD); corpus callosum; memory; attention

1. Introduction

Higher alcohol consumption contributes to a number of structural brain abnormalities, especially in the frontal lobes [1–3] and limbic system [4]. Most often the callosal damage occurs in the form of the Wernicke's encephalopathy [5], the Korsakoff's syndrome [6], the alcohol-related dementia, and the Marchiafava–Bignami disease [7,8]. The corpus callosum is responsible for most of the functional integration and exchange of information between the two cerebral hemispheres [9,10]. In alcohol-dependent individuals with brain structural modifications, the literature has shown reduced volume of the anterior regions [6,11], or all regions [12] of the corpus callosum, as well as smaller cross-sectional area throughout the corpus callosum [13,14] and microstructure abnormalities, such as a lower fractional anisotropy coefficient [15,16].

Alcohol dependence can lead to neuropsychological impairments such as reduction in overall levels of cognition [17], inferior short-term visual and auditory memory [18–20], inferior abstract thinking, inferior working memory, inferior executive functions [21–23], thinking with a predominance of pseudoreminiscence [24], uninhibited and apathetic emotional disorders, as well as loss of emotional control [25]. Studies have shown that individuals with alcohol use disorder have smaller callosal area [26], and that there is a significant correlation between smaller corpus callosum area and cognition [27].

In this study, we use only the visual attention difficulties and memory profile of men, in order to minimize the sample heterogeneity [28]. Many studies have pointed to statistically significant differences between alcohol-dependent men and women, and to gender-specific differences in the toxic effects of ethanol on the body and brain [29–31]. Moreover, the differences of neuropsychological impairment between male and female can also be observed in other central nervous system diseases [32]. It may be

Table 1. Alcohol consumption and control variables.

Variables	Median (IQR)	Range
Duration of abstinence [days]	37 (21–61)	2–182
Duration of alcohol abuse [years]	12 (7–20)	2–40
Severity of alcohol use disorder [MAST score]	37 (29–45)	6–80
Daily alcohol consumption [EtOH gram]	162 (110–309.5)	32–1340
ACE-III score	93 (89–97)	64–100
M-ACE score	27 (24–29)	12–30
Education [years]	12 (11–12)	8–17

Note. EtOH gram of daily alcohol consumption means the amount, in grams, of pure ethanol in an alcohol product. Reference quantities are 16 g EtOH / 50 mL vodka, 11.9 g EtOH / 330 mL beer (according to the Polish State Agency for the Prevention of Alcohol-Related Problems (PARPA). Key: ACE-III, The Addenbrooke's Cognitive Examination; M-ACE, Mini-Addenbrooke's Cognitive Examination; MAST, Michigan Alcoholism Screening Test; IQR, the interquartile range.

important to determine the attention and memory profiles of alcohol-dependent men and women both jointly and separately [11,22,33,34].

The objective of this study was to determine whether there is principal and interaction impact of visuospatial and auditory-verbal memory (whether disordered and normal) on alcohol consumption and brain variables (area of corpus callosum subregions, total corpus callosum area) in men with alcohol use disorder. Additionally, among all alcohol-dependent men the relationships between visual attention, memory and the structural changes in cross-sectional corpus callosum were examined.

2. Subjects and Methods

We screened men with alcohol use disorders and carried out neuropsychological and neuroimaging studies of them in the period from August 2018 to September 2019. The studies were carried out jointly several medical centres. Image acquisition was performed on two sites, the first of which was equipped with an Optima 360 1.5 T magnetic resonance imaging (MRI) machine (GE Healthcare, Milwaukee, WI, USA) and the second one with a Philips Intera Achieva 3.0 Tesla system (Philips Medical Systems, Eindhoven, Netherlands).

2.1 Subjects

One hundred and three men were diagnosed with alcohol dependence syndrome (ICD-10 F.10.2). Six were excluded after data analysis (five on the basis of corpus callosum area analysis and one due to a significantly differentiated neuropsychological profile), leaving 97 men with alcohol use disorders aged from 26 to 59 (Med = 43, M = 43.3, standard deviation (SD) = 8.35). We employed a structured interview, in compliance with the ICD-10 diagnostic criteria, to qualify patients. In doubtful cases, the strength of alcohol dependence in the patients was verified in consultation with a psychiatrist and additionally using an interview employing the diagnostic criteria for alcohol dependence from the DSM-5.

The subjects were recruited in line with the inclusion and exclusion criteria. The inclusion criteria comprised a diagnosis of alcohol dependence, according to the ICD-10 or DSM-5 criteria, and age between 26 and 59. The exclusion criteria were current use of other psychoactive substances, normal intake of neuroleptics due to other mental disorders or behaviour, somatic disease not resulting from an alcohol addiction, or post-accident brain dysfunction (without medical documents or non-clarifying explanation by the subjects).

Patients with neurological disorders (such as dementia, multiple sclerosis, stroke, brain cancer, or other neurodegenerative diseases) or psychiatric disorders (e.g., schizophrenia, bipolar disorder, or major depression) were not included in the study. Nevertheless, eight individuals (8.2%) have suffered epileptic attacks during the persistence of alcohol use disorder; a further eighteen (18.5%) have previously struggled with disorders related to the use of other psychoactive substances — mainly stimulants and cannabis, though often only in small amounts in the past (occasionally at a party, according to the review) or significantly less than alcohol consumption, while 74 (78.7%, N = 94) were addicted to nicotine. Eight (8.3%) of all subjects likely suffered some injuries or microinjuries in the head, though this was unknot confirmed in the medical documentation. Patients' medical histories were checked during interviews, and also after the neurologist, psychiatrist, other clinical psychologist, or nurse had consulted with the patient. According to the patients' medical documentation, 18 of them (18.6%) had struggled with hypertension, 11 of the total number (11.3%) had another somatic disorder, such as asthma or pancreatitis, and 7 of the total number (7.2%) had some other illness, though lacking earlier medical consultation.

According to the demographic data 62 patients (63.9%) were unknot married. Right-handed were 85 patients (87.6%), whereas 5 patients (5.2%) were both left- and right-handed and, 7 patients (7.2%) were only left–handed. Table 1 shows the characteristics of the alcohol-dependent individuals.

The patients' drinking history shows that 49 (53.8%, $N = 91$) grew up in a family with an alcohol problem (heavy drinking present in at least one of their parents or other person in family). Sixty six (68.1%) of examined individuals showed a steady addiction process, beginning with occasional drinking and developing into binge drinking; 24 alcohol-dependent individuals (24.7%) started drinking as a result of a critical life event, such as divorce, job loss, disease, or death of a beloved person; 6 (6.2%) stated that loneliness played a significant role, and one person stated that a predominant chronic stress was the reason he started drinking. The type of alcohol consumed was usually beer and vodka (49; 50.5%) or surrogate alcohol (9; 9.3%); some of the subjects made use of one type of alcohol (25; 25.8%), or three or more different types (14; 14.4%).

Two scanners were used for the neuroimaging examination. Twenty patients were examined using an Optima 360 1.5 T MRI machine (GE Healthcare, Milwaukee, WI, USA) while seventy-seven were examined using a Philips Intera Achieva 3.0 Tesla system (Philips Medical Systems, Eindhoven, Netherlands).

The screening was carried out jointly carried out with specialists working at the treatment and assistance centres. The neuroimaging examination was carried out by a team of specialists at two medical centres in the City of Poznań. The neuropsychological examination was carried out by the lead investigator and a psychologist at the Addiction Treatment Department. All subjects gave their written consent for participation in the study, satisfying the local Ethics Committee (Faculty of Psychology and Cognitive Science at the Poznań-based Adam Mickiewicz University).

2.2 Methodology

All patients were covered by the screening research project, where we collected demographic and alcohol consumption data and information on the strength of alcohol use disorders in the form of Michigan Alcoholism Screening Test (MAST) scores [35,36]. Data was also collected by means of neuropsychological and neuroimaging studies.

2.2.1 Memory and Visual Attention Test Measure

The neuropsychological profile of men with alcohol use disorder — including memory processes, and visual attention — were taken into account by the study.

The California Verbal Learning Test [37] (CVLT; original version [37]) was used to assess short-term auditory memory and auditory-verbal attention. The Polish adaptation was prepared by Emilia Łojek and Joanna Stańczak [38]. The ten indicators in the study are related to the four Jacobus Donders factors [39] and include (1) attention span (List A Trial 1, List B); (2) learning efficiency (List A Trial 5, List A Trial 1–5 total); (3) delayed memory (short-delay free recall, short-delay cued recall, long-delay free recall, long-delay cued recall, and recognition hits); and (4) inaccurate memory (perseveration errors).

The Hillers' Diagnostic Test for Brain Damage (DCS, Diagnosticum für Cerebralschädigung; used in the Polish translation [40] of original version [41]) was used to assess memory capacity during the learning of figural material. The study included three indicators: short-term visual memory range (Trials 1–6 total), encoding new material and attention span (Trial 1), and learning efficiency (Trial 6).

The Brickenkamp's d2 Attention test in the Dajek's 2012 Polish adaptation [42], took into account the results of three indicators: visual attention range (the result of all answers less total errors), ability to concentrate, and total number of errors.

2.2.2 MRI Acquisition

Two scanners were used for the neuroimaging examination: Optima 360 1.5 T MRI scanner (GE Healthcare, Milwaukee, WI, USA) and a Philips Intera Achieva 3.0 Tesla system (Philips Medical Systems, Netherlands). The whole-brain imaging included 3D T1-weighted sequences from the 1.5 T scanner, such as fast spoiled gradient echo (Fast Spoiled Gradient Echo parameters: echo time (TE) = 4 ms; time to repetition (TR) = 10 ms; flip angle = 12°; slice thickness = 1.2 mm, voxel diameters = 1 × 1 × 1.2 mm; pixel bandwidth = 31.2 kHz; field of view (FOV) = 256 × 256 mm) and 3 T scanner (3D turbo fast echo parameters: TE = 4 ms; TR = 8 ms; flip angle = 8°; slice thickness = 1 mm, voxel diameters = 2 × 0.9 × 1 mm; pixel bandwidth = 190 Hz; FOV = 230 × 230 mm). MRI scans of the 3D T1-weighted images from the 1.5 T and 3 T scanners were performed in the oblique plane, and scanning time was about from 8 to 13 minutes for each T1-weighted sequence. The scanning range for both scanners was from the scalp to the skull base, and the patient was in the head first–supine position. All MRI scans were performed by examined neuroradiologist and trained MRI technicians.

2.2.3 Image Processing

Analysis carried out using a Linux–based operating systems (Ubuntu 16.04 LTS/Xenial, Canonical Ltd./Ubuntu Foundation, San Francisco, CA, USA). T1–weighted sequences were analysed in compliance with the MRI programs hints using scripting languages (Python 3.6.10, Python Software Foundation, Wilmington, DE, USA). In Step One, the resulting T1–weighted sequence files in Digital Imaging and Communications in Medicine (DICOM) format were converted into the Neuroimaging Informatics Technology Initiative (NIFTI) format; anonymization was also carried out for the follow-up structural analyses. The data from 1.5 T scanner was con-

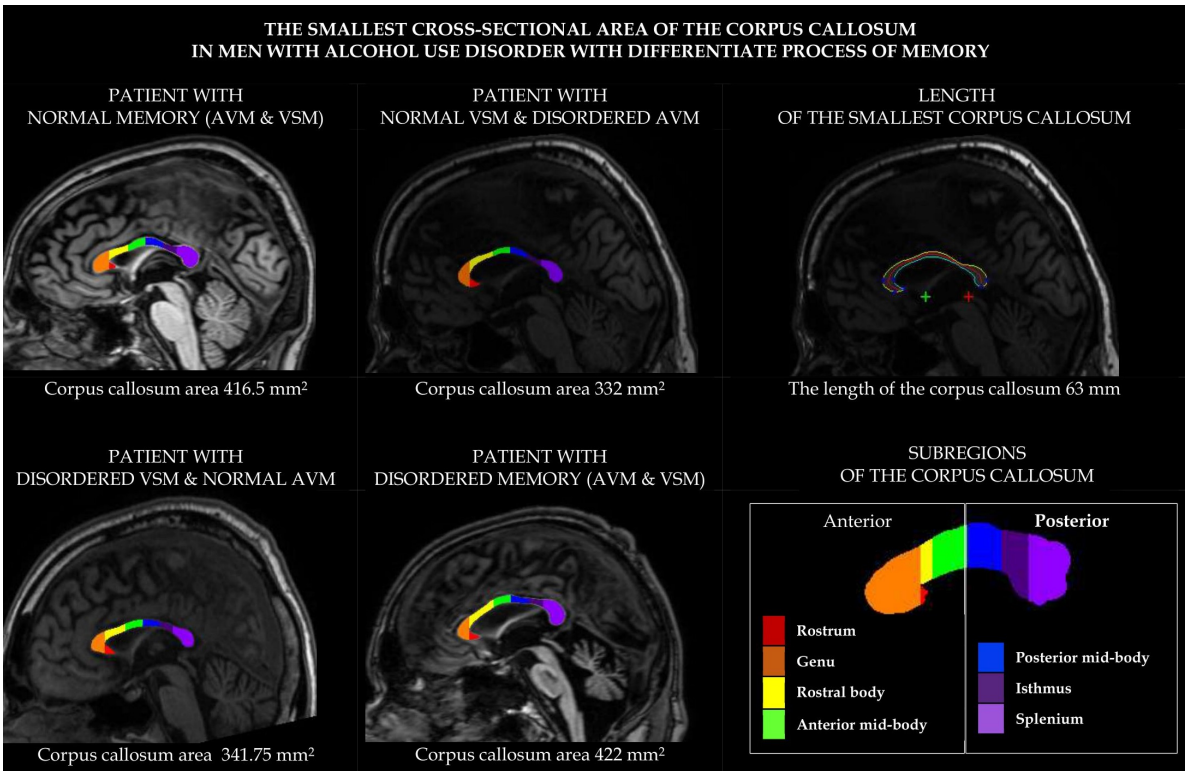

Fig. 1. Segmentation of the corpus callosum. Witelson segmentation of the corpus callosum in the midsagittal plane with seven subdivisions from anterior to posterior. T1-weighted MRI scan of the males with alcohol use disorder who had the smallest total corpus callosum depending on the level of memory disorders. MRI, magnetic resonance imaging.

verted using MRIConvert 2.0 (Lewis Center of Neuroimaging, Eugene, OR, USA); data from 3 T scanner was converted using MRIcroGL 2018 (NeuroImaging Tools & Resources Collaboratory, Department of Health and Human Services, USA; https://www.nitrc.org/projects/mricrogl/). In Step Two the structural analysis was carried out using the FMRIB Software Library v. 6.0 (FMRIB, Oxford, UK) [43]. Volumetric measurements of grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF), were taken using FMRIB's Automated Segmentation Tool [44] with the skull-stripped T1-weighted sequences, obtained using Brain Extraction Tool [45]. The automatic corpus callosum segmentation was performed on the basis of the 3D structural T1-weighted sequences (raw data in NIFTI format) using yuki 2.1 – 1.6.3, part of Automatic Registration Toolbox, according to Babak Ardekani [46]. The yuki tool was used to segment automatically a corpus callosum midsagittal cross-sectional area; the 1.5 T scanner data for three subjects was manually corrected, but ultimately was not included in the follow-up analysis, due to outliers. The cross-sectional area of the whole corpus callosum, its length, circularity, and perimeter were distinguished, as well as the cross-sectional area of the corpus callosum regions from the anterior to the posterior: the rostrum (W1 region), genu (W2 region), rostral body (W3 region), anterior mid-body (W4 region), posterior mid-body (W5 region), isthmus (W6 region), and splenium (W7 region). The Sandra Witelson's [47] scheme for segmenting the corpus callosum into regions was used (see Fig. 1). In the figure below, the segmentation of the corpus callosum cross-sectional area was introduced.

2.3 Statistical Analysis

Due to the numerous indicators used in each memory test, the composite Z-score for memory standardized variable was measured. To minimize type 1 errors, the composite Z-score for each functional domain was computed by adding up the Z-score of all measures included in that composite. The MEMORY included the Z-scores of four indicators (CVLT: Trials 1–6 total, Short Delay Free Recall, Long Delay Free Recall, DCS: Trials 1–6 total). Higher values of composite scores indicated better performance, and lower Z-score indicated a worse performance. The ATTENTION domain included the ability to concentrate and Z-scores visual attention range.

Because there was only one heterogeneous group, we carried out an explanatory analysis and multiple comparisons. Each variable was evaluated using a Shapiro-Wilk normality test. For non-normally distributed continuous variables, we used the Spearman's rho correlation coefficient (nonparametric statistics); otherwise, the Pearson *r* correlation coefficient for normally distributed continuous variables was employed. To minimize type 1 errors, the False Discovery Rate (FDR) method was used as a correc-

Table 2. Descriptive statistics of the neuropsychological variables.

Neuropsychological and neuroimaging variables			Mean (SD) or [a] median (IQR)	Range of raw data	Range compared to standardized scores from low to high[#]
Memory (auditory–verbal and visuospatial): MEMORY composite scores					
Learning efficiency (CVLT test: List A–Trial 1–5 Total)			45.43 (9.98)	26–74	Sten scores: 1–9 (10)[##]
Delayed memory (CVLT test: Short Delay Free Recall)			9.61 (3.13)	0–16	Sten scores: 1–10
Delayed memory (CVLT test: Long Delay Free Recall)			10 (7–12)[a]	0–16	Sten scores: 1–10
Visual memory range/Learning efficiency (DCS test: Trials 1–6 Total)			26.33 (10.91)	3–52	Stanine scores: 1–9
Memory (auditory–verbal and visuospatial): not in MEMORY composite scores					
Learning efficiency (DCS test: Trial 6)			6 (4–8)[a]	0–9	Stanine scores: 1–9
Learning efficiency (CVLT test: List A Trial 5)			11 (9–13)[a]	6–16	Sten scores: 1–10
Delayed memory (CVLT test: Short Delay Cued Recall)			11 (9–12)[a]	5–16	Sten scores: 1–10
Delayed memory (CVLT test: Long Delay Cued Recall)			10.64 (2.71)	4–16	Sten scores: 1–10
Attention: ATTENTION composite scores					
Visual attention range (d2 test)			354.52 (107.24)	109–583	Stanine scores: 1–9
Ability to concentrate (d2 test)			126.12 (48.47)	0–255	Stanine scores: 1–9
Volumetric measurements					
Brain parenchymal fraction			76.86 (1.88)	72–82	–
Corpus callosum cross–sectional area					
Corpus callosum area [mm^2]			568.77 (91.04)	332–810	–
Corpus callosum length [mm]			70 (4.28)	59–79	–
Corpus callosum perimeter [mm]			198.27 (13.85)	169–234	–
Corpus callosum circularity [mm]			0.18 (0.025)	0.12–0.25	–
Corpus callosum subregions (segments) [mm^2]:					
W1	Rostrum	Orbital prefrontal cortical region	24.36 (7.06)	9.25–45	–
W2	Genu	Prefrontal cortical region	123.98 (26.67)	71–180	–
W3	Rostral body	Premotor cortical region	85.45 (14.73)	52–121	–
W4	Anterior mid-body	Motor cortical region	64.50 (11.14)	34–87	–
W5	Posterior mid-body	Posterior parietal cortical region	57.29 (10.94)	34–91	–
W6	Isthmus	Superior temporal cortical region	48.75 (39.75–56.13)[a]	20–89	–
W7	Splenium	Occipital cortical region	164.27 (28.27)	89–239	–

Note. [#] for sten scores, low raw results are assigned a value from 1 to 3, medium raw results are assigned a value from 4 to 7, and high raw results are assigned a value from 8 to 10; for stanine scores, low raw results are assigned a value from 1 to 3, medium raw results are assigned a value from 4 to 6, and high raw results are assigned a value from 7 to 9; [##] results of standardized scores for individuals with two different age ranges, in accordance with standardization tables in manuals of memory tests; [a]median (IQR). CVLT, The California Verbal Learning Test; DCS, Diagnosticum für Cerebralschädigung; SD, standard deviation.

tion of the two-tailed multiple correlation analysis. Statistically significant relationships were taken into account in multiple regression, correcting for age analysis, especially to assess the impact of the corpus callosum area (independent predictors) on the composite scores.

To verify the hypotheses, the memory results were compared with the standardized values available in age tables provided in the Polish version of the test manuals (CVLT test: Tables I–III and V–VI, DCS test: Table 11a). The raw data was coded as "0" (below normal test result; disorder) and "1" (normal test result). In Step Two, the memory profiles (normal vs. disordered) were compared using multivariate analysis of variance (MANOVA).

Because we applied two scanners, we decided to determine whether the corpus callosum cross-sectional area results differed with the scanner. A statistical analysis was performed using the SPSS v 27.0 (IBM SPSS, Armonk, NY, USA).

3. Results

3.1 Descriptive Statistics for Neuropsychological Variables

The chart box of variables shows that a number of outliers occurred. Two outliers were seen among the indicators of auditory-verbal memory. There were four other outliers for the corpus callosum. We decided not to include all indicators of neuropsychological test and so removed six outliers. The number of examined subjects was then equal to ninety seven. Descriptive statistics are presented in Table 2.

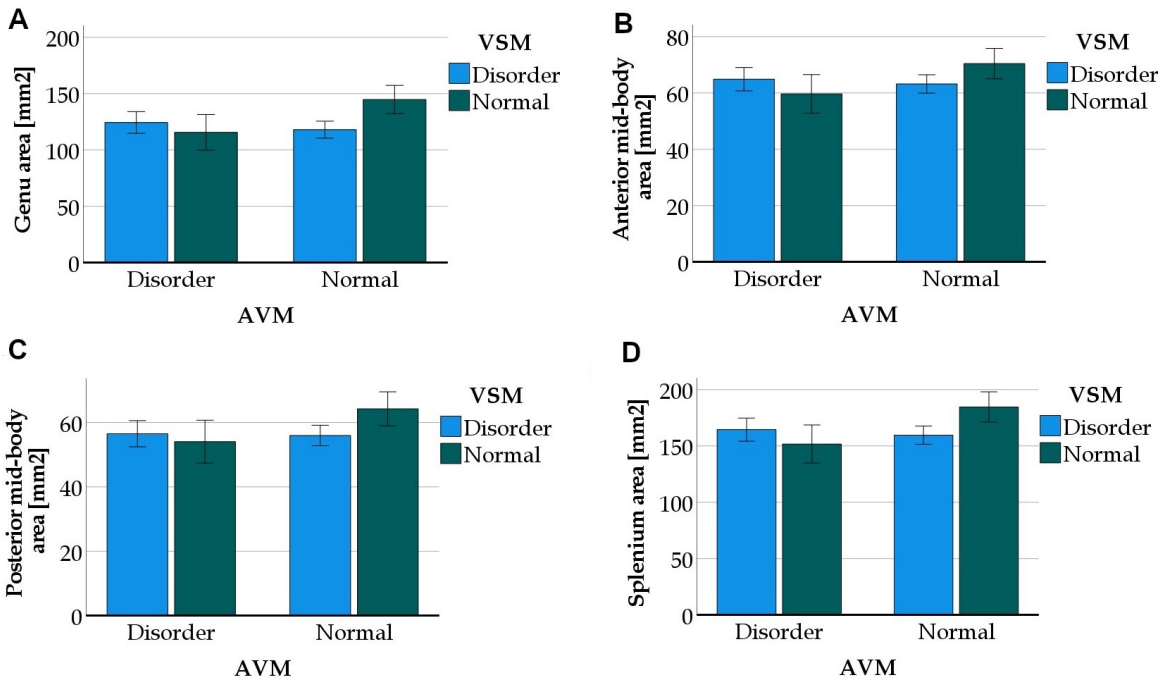

Fig. 2. Corpus callosum regions in both groups (AVM and VSM). Bar graphs (with 95% CI) of the corpus callosum regions and the memory profile (normal vs. disordered) in both the AVM and VSM groups. The results were compared to age-adjusted normative values. (A) Cross-sectional of genu area in patiens with normal and disordered memory; (B) Cross-sectional of anterior mid-body area in patiens with normal and disordered memory; (C) Cross-sectional of posterior mid-body area in patiens with normal and disordered memory; (D) Cross-sectional of splenium area in patiens with normal and disordered memory. 95% CI, 95% Confidence interval; AVM, auditory-verbal memory; VSM, visuospatial memory.

The individuals' results range from low to high, indicating a very broad range of cognitive capacity, from normal to disordered. The mean raw data, after comparison, is equivalent to a point in the middle of the standardized scores — excluding memory processes, which range from low to medium.

3.2 Comparisons of Two Scanner Results

There were no statistically significant ($p > 0.05$) differences between the results received from the 1.5 T and 3 T scanners for the cross-sectional area of the whole corpus callosum, the length of the corpus callosum, or any of its regions (W1–W7), but there were statistically significant differences related to the perimeter ($F = 4.61$, $p = 0.034$), and circularity ($F = 7.23$, $p = 0.008$) of corpus callosum.

3.3 Alcohol-Dependent Men with Normal and Disordered Memory

The Polish versions of the neuropsychological tests allow normal and disordered memory range to be distinguished. We decided to introduce DCS Trials 1–6 total of visuospatial memory (VSM group) and CVLT Trials 1–5 total of auditory-verbal memory (AVM group) separately. Both groups are described in Table 3 (mean and standard deviation or median and interquartile range).

3.3.1 Alcohol Consumption and Education Variables

MANOVA revealed a statistically significant main effect of the VSM group for education [$F(1, 97) = 9.51$, $p = 0.003$, $h^2 = 0.093$], daily alcohol consumption [$F(1, 87) = 4.60$, $p = 0.035$, $h^2 = 0.052$], alcohol abuse duration [$F(1, 97) = 6.21$, $p = 0.014$, $h^2 = 0.063$], and severity of alcohol use disorder as the MAST score [$F(1, 97) = 4.22$, $p = 0.043$, $h^2 = 0.043$]. Pairwise comparisons of VSM group (with normal and disordered levels of this memory) showed that the VSM disorder group was characterized with lower education background, had longer alcohol abuse duration, had more severe alcohol use disorder, and had the highest frequency of daily alcohol consumption. There was no significant main impact of the AVM group and no interaction effect of both groups. The duration of abstinence did not reveal a significant principal effect in each group.

3.3.2 Cross-Sectional Area of Corpus Callosum Regions

MANOVA revealed a statistically significant main impact of the AVM group for the cross-sectional area of the splenium of the corpus callosum ($F(1, 97) = 4.86$, $p = 0.030$, $h^2 = 0.050$). Pairwise comparisons show that those with AVM disorder had smaller splenium areas than those with normal AVM. Despite the lack of statistically significant principal effect of the VSM group, an interaction effect of the AVM and VSM groups was observed for the cross-

Table 3. Demographic and alcohol consumption characteristics of the alcohol use disorder category.

Men with alcohol use disorder (with normal or disordered memory)	N [%]	Age [years]	Education [years]	ACE-III	Duration of abstinence [days]	Abuse duration [years]	Severity of use disorder [MAST score]	Daily consumption [EtOH gram]
Auditory-verbal Memory (AVM)								
AVM disorder	37 (38)	42 (7.84)	12 (11–12)[a]	91 (88–95)[a]	47.92 (26.96)	12 (8–25)[a]	36.65 (12.63)	162 (112–267)[a]
AVM normal	60 (62)	44 (8.67)	12 (11–12)[a]	95 (90–97)[a]	30 (21–61)[a]	12 (7–20)[a]	37 (29–45)[a]	168 (109–320)[a]
Visuospatial Memory (VSM)								
VSM disorder	71 (73)	44 (8.64)	12 (11–12)[a]	91 (88–95)[a]	31 (21–61)[a]	15 (8–23)[a]	37.89 (12.35)	214 (152–320)[a]
VSM normal	26 (27)	41 (6.91)	12 (12–17)[a]	97 (93–99)[a]	47.15 (24.07)	11.19 (6.51)	31.12 (13.06)	139 (88–217)[a]

Note. [a]median and IQR.

Table 4. Demographic and alcohol consumption characteristics of the interaction groups with alcohol use disorder.

Men with alcohol use disorder (Interaction Group)	N	Age [years]	Education [years]	Duration of abstinence [days]	Abuse duration [years]	Severity of use disorder [MAST score]	Daily consumption [EtOH gram]
AVM disorder & VSM disorder	27	43 (8.48)	12 (11–12)[a]	46 (28.42)	16 (8–28)[a]	38 (13.82)	162 (128–315)[a]
AVM disorder & VSM normal	10	41 (5.77)	12 (11–13)[a]	53 (23.02)	9 (4.94)	34 (8.82)	176 (86.66)
AVM normal & VSM disorder	44	45 (8.76)	12 (11–12)[a]	30 (21–61)[a]	14 (5.5–20)[a]	38 (11.52)	228 (160–320)[a]
AVM normal & VSM normal	16	41 (7.71)	12 (12–17)[a]	43 (24.61)	12 (7.25)	29 (15.05)	136 (90.94)

Note. [a] Median and IQR; AVM, Auditory-Verbal Memory; VSM, Visuospatial Memory.

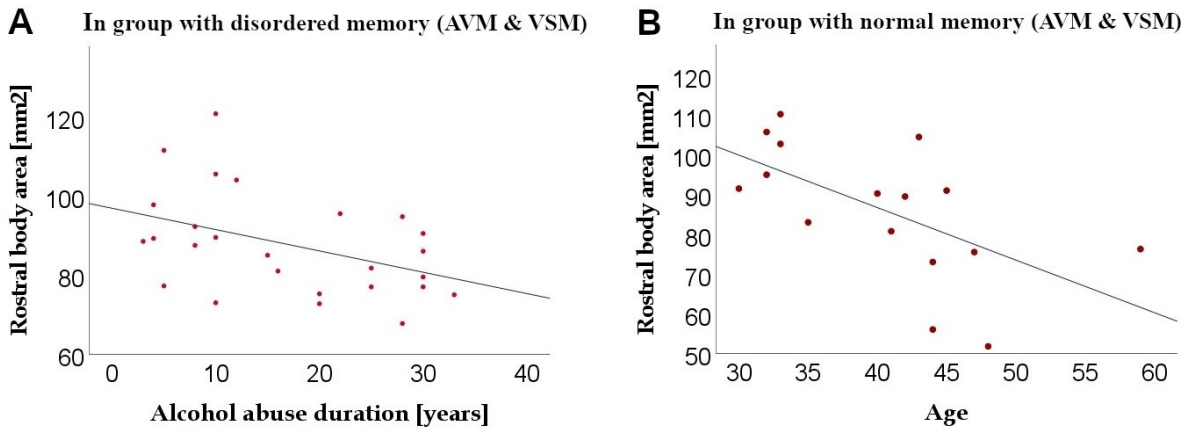

Fig. 3. A regression plots related to patients with normal and disordered memory. (A) Alcohol abuse duration vs. Rostral body atrophy; (B) Age vs. Rostral body atrophy.

sectional area of the regions of the corpus callosum, such as the genu ($F(1, 97) = 8.93$, $p = 0.004$, $h^2 = 0.088$), the anterior mid-body ($F(1, 97) = 5.86$, $p = 0.017$, $h^2 = 0.059$), the posterior mid-body ($F(1, 97) = 4.60$, $p = 0.035$, $h^2 = 0.047$), and the splenium ($F(1, 97) = 8.86$, $p = 0.004$, $h^2 = 0.087$). The data on the interaction effect are presented in Fig. 2.

MANOVA revealed a statistically significant principal interaction effect of AVM and VSM group for the total corpus callosum cross-sectional area ($F(1, 97) = 6.95$, $p = 0.010$, $h^2 = 0.070$). Pairwise comparisons showed that both the normal AVM and VSM groups had larger total corpus callosum area.

3.4 Multiple Correlations in the Four Groups of Men

Taking into account the results of MANOVA analyses we decided to verify the relationships between control and alcohol consumption variables and cross-sectional subregions area of the corpus callosum. First, the descriptive statistics (mean and standard deviation or median and interquartile range) of the four groups of alcohol-dependent men are introduced below (see Table 4).

3.4.1 Disordered AVM and Disordered VSM

The results initially pointed to a statistically significant correlation between the alcohol abuse duration and length of the corpus callosum ($rho(27) = 0.406$, $p = 0.036$, $FDR = 0.162$), and its subregional area — rostral body ($rho(27) = 0.406$, $p = 0.036$, $FDR = 0.162$). There was no statistically significant relationships ($p > 0.05$) between the age, level of education, other alcohol consumption variables and cross-sectional area of the corpus callosum.

A multiple regression analysis correcting for age and kind of scanner was carried out. Only the alcohol abuse duration was statistically significant predictor ($\beta = –0.538$; $p = 0.026$) of the rostral body of the corpus callosum. The model accounted for 21% of the variance. The results were shown in Fig. 3.

3.4.2 Disordered AVM and Normal VSM

The results pointed initially to a statistically significant correlation between the lower level of education and smaller cross-sectional area of the corpus callosum ($rho(44) = 0.336$, $p = 0.026$, $FDR = 0.117$) and its subregional area - splenium ($rho(44) = 0.420$, $p = 0.005$, $FDR = 0.045$). There was no statistically significant relationships ($p > 0.05$) between the age, alcohol consumption variables and cross-sectional area of the corpus callosum.

A multiple regression analysis correcting for age and kind of scanner was carried out. The level of education wasn't statistically significant predictor ($\beta = 0.118$; $p = 0.473$) of the splenium of the corpus callosum.

3.4.3 Normal AVM and Disordered VSM

There were statistically significant relationship between the smaller cross-sectional area of the corpus callosum and higher severity of alcohol use disorder ($r(10) = –0.642$, $p = 0.045$, $FDR = 0.108$) only in alcohol-dependent individuals with disordered auditory-verbal memory. In the posterior part of the corpus callosum, we observed correlations between the higher severity of alcohol use disorder (MAST score) and smaller isthmus ($r(10) = –0.644$, $p = 0.045$, $FDR = 0.108$) and splenium ($r(10) = –0.674$, $p = 0.033$, $FDR = 0.108$). There was no other statistically significant relationships ($p > 0.05$) between the age, level of education, alcohol consumption variables and cross-sectional area of the corpus callosum.

A multiple regression analysis correcting for age and kind of scanner was carried out. The severity of alcohol use disorder wasn't statistically significant predictor ($\beta = –0.591$; $p = 0.060$) of the splenium of the corpus callosum.

3.4.4 Normal AVM and Normal VSM

We verified a statistically significant relationships between the age and rostral body of corpus callosum cross-sectional area ($r(16) = –0.606$, $p = 0.013$, $FDR = 0.117$).

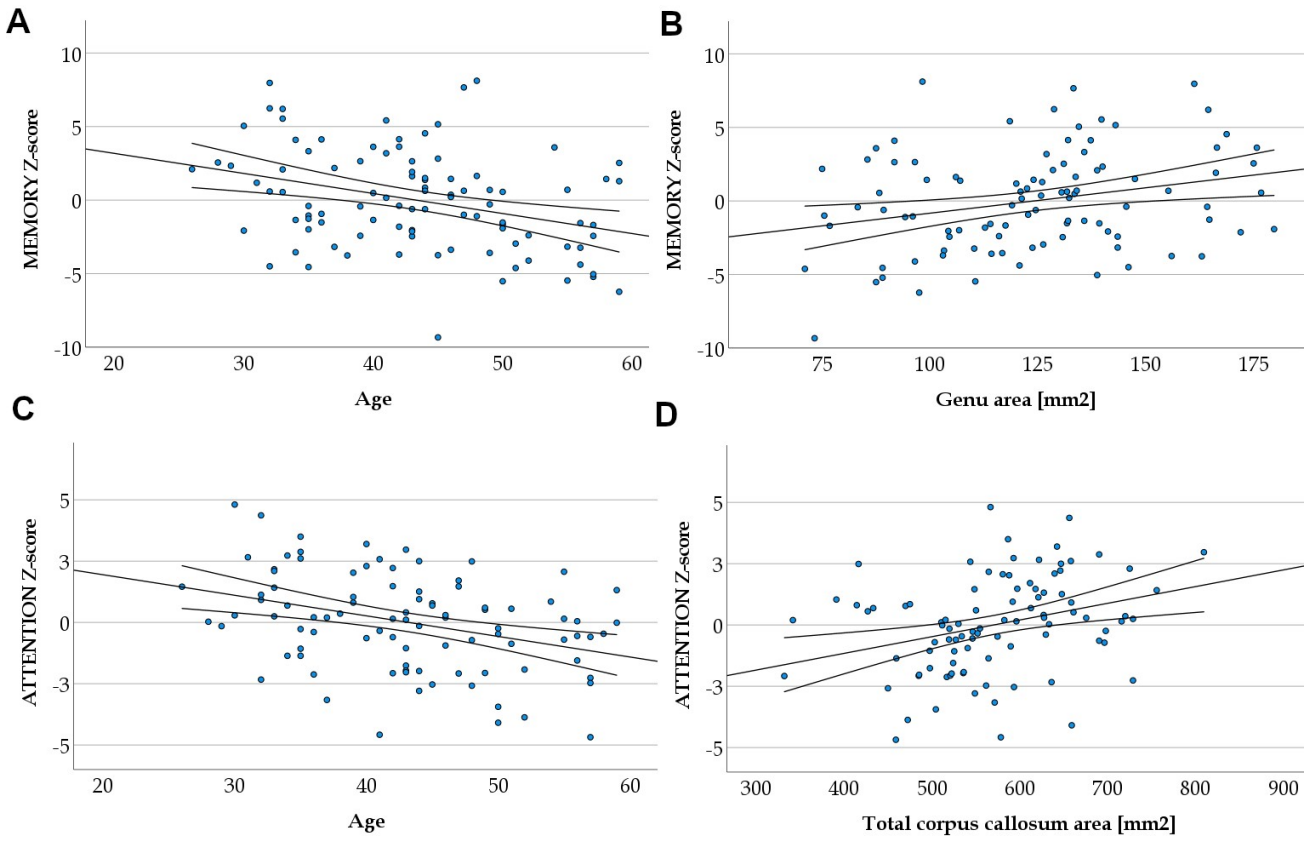

Fig. 4. A regression plots with 95 % CI. (A) Age vs. Memory Z-score; (B) Genu area vs. Memory Z-score; (C) Age vs. Attention Z-score, (D) Total corpus callosum area vs. Attention Z-score. 95 % CI, 95 % confidence interval.

There was no statistically significant relationships between the level of education, alcohol abuse duration, alcohol daily consumption, abstinence, the severity of alcohol use disorder and cross-sectional area of the corpus callosum, its length and its sub-regions (genu, rostrum, rostral body, anterior mid-body, posterior mid-body, isthmus, splenium) in alcohol-dependent men with normal memory ($p > 0.05$).

A multiple regression analysis correcting for scanner type was carried out. The older age was a statistically significant predictor (β = –0.599; p = 0.020) of the smaller rostral body of the corpus callosum. The model accounted for 37 % of the variance. The results were shown in Fig. 3.

3.5 Multiple Correlations between Composite Scores and the Cross-Sectional Area of the Corpus Callosum

First, there was a statistically significant correlation between composite scores, ATTENTION vs. MEMORY ($r(93)$ = 0.50, $p < 0.001$). Second, the results initially pointed to a statistically significant correlation between the corpus callosum cross-sectional area and the ATTENTION score ($r(93)$ = 0.31, p = 0.002, FDR = 0.008). Third, there was marginally significant relationship between the total corpus callosum area and MEMORY score, and there was no statistically significant relationship between the length of the corpus callosum and composite Z-scores. We also verified a relationship between the cross-sectional area of the particular regions of the corpus callosum (rostrum, genu, rostral body, anterior mid-body, posterior mid-body, isthmus, splenium).

In the frontal part of the corpus callosum, the smaller cross–sectional area of the genu of the corpus callosum was associated with lower MEMORY ($r(97)$ = 0.27, p = 0.007, FDR = 0.048) and ATTENTION scores ($r(93)$ = 0.28, p = 0.006, FDR = 0.012); the smaller anterior mid-body of the corpus callosum was more weakly related to lower MEMORY scores ($r(97)$ = 0.24, p = 0.018, FDR = 0.048), and strength correlated with lower ATTENTION scores ($r(93)$ = 0.33, p = 0.001, FDR = 0.008).

In the posterior part of the corpus callosum**,** we observed a strong correlation between the posterior mid-body of the corpus callosum and the ATTENTION scores ($r(93)$ = 0.30, p = 0.004, FDR = 0.011), and a weak relationship with MEMORY scores ($r(97)$ = 0.25, p = 0.015, FDR = 0.048); the smaller isthmus was associated with ATTENTION scores ($rho(93)$ = 0.28, p = 0.008), and the smaller splenium was also correlated with lower ATTENTION scores ($r(93)$ = 0.24, p = 0.022, FDR = 0.035).

Age correcting multiple regression analysis has indicated which cross-sections can predict the cognitive composite scores. Modelling MEMORY scores indicated that age (β = –0.284, p = 0.005) and genu area (β = 0.199, p

Table 5. The Pearson r or Spearman rho coefficient of subregional corpus callosum area and memory indicators.

Corpus callosum sub-regions [mm^2]	Visuospatial memory (VSM)		Auditory–verbal memory (AVM)					
	Learning efficiency		Learning efficiency		Delayed memory			
	Trials 1– 6 total	Trial 6	Trials 1– 5 total	Trial 5	SDFR	SDCR	LDFR	LDCR
Anterior CC								
Rostrum	0	–0.01[a]	–0.03	–0.06[a]	–0.03	–0.08[a]	–0.09[a]	–0.07
Genu	**0.27**	**0.34**[a]	0.17	0.22[a]	0.25	0.23[a]	0.22[a]	**0.24**
Rostral body	0.01	0.06[a]	–0.07	0.02[a]	0	0.03[a]	0.02[a]	0.02
Ant. mid-body	0.2	**0.29**[a]	0.18	0.23[a]	0.19	0.22[a]	0.23[a]	**0.24**
Posterior CC								
Post. mid-body	0.22	**0.28**[a]	0.18	0.18[a]	0.2	0.19[a]	0.21[a]	0.2
Isthmus	**0.22**[a]	**0.30**[a]	0.09[a]	0.12[a]	0.08[a]	0.03[a]	0.12[a]	0.07[a]
Splenium	0.19	**0.23**[a]	0.09	0.14[a]	0.1	0.12[a]	0.20[a]	0.13

Note: Statistically significant and marginally significant correlation coefficients and p-values are in bold ($p \leq 0.05$), [a] Spearman rho coefficient.
Key: Ant. mid-body, Anterior mid-body; Post. mid-body, Posterior mid-body; SDFR, Short Delayed Free Recall; SDCR, Short Delayed Cued Recall; LDFR, Long Delayed Free Recall; LDCR, Long Delayed Cued Recall; CC, Corpus Callosum.

= 0.046) were predictors. For MEMORY scores, the age and smaller genu areas accounted for 13% variance. Modeling the ATTENTION scores indicated that both age ($\beta = -0.307$, $p = 0.002$) and total corpus callosum area ($\beta = 0.255$, $p = 0.010$) were predictors, accounting for 17 % variance. The results were shown in Fig. 4.

3.6 Multiple Correlations between the Components of Auditory-Verbal and Visuospatial Memory and the Corpus Callosum Area

Given that the memory process has various components, we decided to examine the relations between the corpus callosum regions of interest (ROI) and components of visuospatial and auditory-verbal memory. The results of trials Nos. 1–5 of auditory-verbal memory included one additional outlier. The Pearson r and Spearman rho correlation coefficients, with FDR correction, were calculated and are presented in Table 5.

There was no statistically significant correlation between attention span (Trial 1 of visuospatial memory and Trial 1, Trial B of an auditory-verbal memory) and the data from our analysis of the corpus callosum's regions. Due to the many relationships between Trial 6 of visuospatial memory and the regions of the corpus callosum, a multiple regression analysis correcting for age was carried out. Modeling Trial 6 of the DCS scores from the corpus callosum ROI indicated that age ($\beta = -0.303$; $p = 0.002$) and cross-sectional area of the genu ($\beta = 0.242$; $p = 0.013$) were predictors. The model accounted for 17% of the variance.

4. Discussion

We report the associations between structural changes in the brain and cognitive impairments in men with alcohol use disorder. The results showed that the early memory disorders (visuospatial and auditory-verbal) may be a factors of corpus callosum atrophy, especially in such subregions as genu, anterior mid-body, posterior mid-body, and splenium. On the other hand, the smaller cross-sectional area of the total corpus callosum is positively associated with a visual attention and the reduced callosal subregion's, genu atrophy, may be responsible for a memory impairment. Other structural changes in the corpus callosum and its subregions were found in this study, and their relationships with memory and attention processes will be discussed.

4.1 Structural Changes in the Corpus Callosum in Alcohol Use Disorder

The corpus callosum is responsible for the information exchange between the two cerebral hemispheres. The range of information exchange is broad, so the corpus callosum structure plays a role in emotional, sensory, memory, attention, executive functions [10], and in some aspects of language functions [48]. Previous studies have reported that the size of the corpus callosum showed lower parameters and ratios in older age categories [49]. Additionally, significant correlations between the older age and corpus callosum atrophy were found in alcohol-dependent patients [50]. The most research indicated on the microstructural changes in the corpus callosum, but in accordance to our aims of study, we focused mainly on the macrostructural changes in the corpus callosum.

4.1.1 Primary Callosal Changes — Role of the Fetal Alcohol Spectrum Disorders in Children

Atypical cortical trajectories with corpus callosum reduction have been observed in fetal alcohol spectrum disorders in children [51–54]. Not only smaller cross-sectional area of the corpus callosum was observed, but also white matter disintegrity e.g. lower value of a fractional anisotropy indicator in posterior tracts of the corpus callosum — the posterior mid-body, isthmus and splenium [55]. As reported, these callosal structural changes will be found in adolescents and adults, who suffered from prenatal alcohol exposure. Previous studies on fetal alcohol spectrum disorders in adults have reported that the brain maturation

may vary from one case to another, and also the corpus callosum, basal ganglia, cerebellum showed smaller volume in earlier age [56]. Our study found callosal morphology alterations in alcohol-dependent men with memory disorders. Especially, the areas of the subregions of the corpus callosum — such as the genu, anterior mid-body, posterior mid-body, and splenium — were seen to be damaged in alcohol-dependent men with memory visuospatial and auditory-verbal disorders. Although, in our study, the potential problem of fetal alcohol spectrum disorders in examined patients did not appear, our results showed that the capacity of memory processes, probably associated with neurodevelopmental changes, may lead to gradual corpus callosum atrophy (in some subregions in particular) in adult men with alcohol use disorders.

4.1.2 Alcohol-Induced Callosal Changes in Adults

The reductions in the corpus callosum area in alcohol-dependent patients with longer abuse duration and greater severity of alcohol consumption are well-known. The most studies pinpointed the structural changes in the brain that were observed in the Korsakoff syndrome, the Wernicke's encephalopathy, the alcohol-related dementia, and the Marchiafava–Bignami disease. First, the smaller corpus callosum, medial thalami, and mammillary bodies were found in the Korsakoff syndrome [6]. Second, there was observed a callosal atrophy with a range from 18.2% to 32.8% reduction in prefrontal callosum subregions in alcohol-dependent patients with the Wernicke's encephalopathy [5]. Third, the cross-sectional area of the corpus callosum was atrophied in the alcohol-related dementia and the Matchiafavy-Bignami disease [57]. On the other hand, Kyle Bullock *et al*. [2] verified that more severe alcohol use disorder was associated with lower grey matter density in the hypothalamus and right superior frontal gyrus, but only in heavy drinking smokers. Nevertheless, other studies have reported that the cross-sectional area of the corpus callosum was reduced in callosal subregions' such as genu, body and splenium, both in men and women with alcohol use disorder; moreover, the life-long alcohol consumption and age of alcohol-dependent men have been a simultaneous predictors of a smaller splenium area [50]. Our study showed that higher age predict the smaller area of the rostral body of the corpus callosum only in alcohol-dependent men with normal memory processes, but the longer alcohol abuse duration drives the reduction of the rostral body area of the corpus callosum in alcohol-dependent men with memory disorder.

4.2 Memory (Normal vs. Disordered) in Alcohol-Dependent Patients

There is growing evidence that corpus callosum atrophy in alcohol-dependent men with normal and disordered memory seem to provide a novel perspective in understanding their memory functioning. Rather than comparing their results to standardized values on the sten, stanine or centile scales, many studies have described visuospatial and auditory-verbal memory difficulties as occurring more frequently in alcohol-dependent individuals than in control groups. We thought that it is important to distinguish the level of patients' memory in relation to age-standardized data, taking into account the role of the cross-sectional area of the corpus callosum (a neural correlate of memory). However, in considering memory processes as both protective factors and risk factors, it was important to verify which aspects of this cognitive function was disordered and which was normal. The protective role of the memory was associated with aspects that was well preserved in patients, results indicated on the role of auditory-verbal memory, which was often on the medium level and maintained its proper psychosocial functioning.

4.2.1 Development of a Memory Disorders

The studies on fetal alcohol spectrum disorders have reported that brain abnormalities may be associated with deficits in memory, visuospatial ability, and other executive and socio-emotional functions [58]. Among children with prenatal alcohol exposure and postnatal risk factors, the differentiation of brain structural changes, including not only corpus callosum atrophy, but also frontal lobes, caudate, putamen, hippocampus and cerebellar vermis dysfunctions, may lead to a broad spectrum of neuropsychological deficits such as intellectual impairment, visual memory disorders, lower visuospatial skills, and difficulties in executive functions, attention and language [59]. Additionally, dysfunction in learning efficiency of the memory processes may be observed in individuals with familiar risk of alcohol use disorder, due to the differences in maturation of higher order association cortices that are crucial to on-going development in executive function and other socio-emotional functions during adolescence [60]. Other studies showed that participants in the age range of 11-25 years, with high risk for alcohol use disorder, characterized by high impulsivity and significantly different executive functions [61].

These neuropsychological profile of children's and adolescents' functioning may lead to further difficulties in memorizing new information, and a reduction in learning efficiency related to the memory processes and some aspects of executive functions. There is a risk that neurodevelopmental disorders will affect adults' functioning and will become more intensified in alcohol-dependent men [62]. Our study found more significantly visuospatial memory disorders than auditory-verbal memory disorders in men with alcohol dependence. Visuospatial memory disorders have often occurred in patients with lower levels of education, longer duration of alcohol abuse, more frequent daily alcohol consumption, and higher severity of alcohol use disorder. We can assume that more intensified alcohol consumption, education negligence (or lack of learning ability) lead to visuospatial memory disorders. Moreover,

in alcohol-dependent men with both memory disorders (visuospatial and auditory-verbal) the corpus callosum atrophy was observed. Based on our research findings, it can be concluded that memory disorders in men with alcohol-dependence may contribute to their inferior functioning, and finally lead to a gradual structural changes in the corpus callosum (especially in the genu, anterior mid-body, posterior mid-body, splenium). The severe memory impairments and higher alcohol consumption may be listed as risk factors such as for loneliness, occupational and leisure time mental inactivity. The inferior mental functioning usually leads to the loss of nerve cells and the gradual atrophy of brain structures [63], including corpus callosum.

4.2.2 Structural Changes in the Brain Related to Memory Disorders and Attention Difficulties

Most studies confirm that the corpus callosum dysfunction and other brain structures was positively related to the cognitive impairments in neurological disease caused by longer alcohol abuse duration. Among other mechanisms, it is resulting from a dysregulation of the dopaminergic system [64]. On the one hand, the corpus callosum atrophy often leads to the memory disorders, especially in auditory-verbal delayed memory [65]. On the other hand, the neural correlates of visual attention in alcohol use disorder indicated on the functional changes in prefrontal or parietal lobes [66]. Our study confirms that there is a positive correlation between a visual attention and memory processes, as in the literature these cognitive domains are interacted [67].

Studies on patients suffering from the Korsakoff syndrome have reported that a reduction in mammillary bodies, thalamus, hypothalamus, basal ganglia, cerebellar vermis and damaged white-matter tracts (partially in genu of the corpus callosum) was responsible for a set of higher-order cognitive dysfunctions, including verbal working memory, immediate and delayed verbal recall, verbal and visual recognition, executive functions, but in attention processes the difficulties was not observed [68]. However, in spite of unclear regional brain dysfunction, verbal memory disorder was seen especially in patients with Korsakoff's syndrome, but not in the non-demented alcoholic patients [69]. What is more, visuospatial abilities (visual attention and visuospatial memory), immediate and delayed auditory-verbal memory, executive functions were declined in alcohol-dependent individuals compared to the control group [18]. Previous research projects on alcohol use disorder have reported that smaller genu and splenium of the corpus callosum are weakly correlated with lower visuospatial recognition (aspect of visual attention), and are not associated with working memory; additionally, the negative correlations between age and callosal area (genu and splenium) were noticed in the alcohol-dependent men population [50]. Our results showed that the memory capacity, whether overall or in terms of the single aspect of visual learning efficiency, has been predicted by age and the genu area , while the lower visual attention processes have been predicted by older age and total corpus callosum atrophy. Additionally, the role of the area of the corpus callosum isthmus has proved to be significant in both visual memory and attention abilities. Moreover, the atrophy of four subregions of the corpus callosum area (genu, mid-body, isthmus, and splenium) are associated with lower visual learning efficiency (Trial 6) and visual attention decline, but only the genu atrophy and older age of alcohol-dependent men were predictors of difficulties in visual learning efficiency.

5. Limitations

One of this study constraints related to the heterogeneous profile of participants, with their broad age range, despite the fact that only men were included. Ultimately, the age of the subjects was to cover a smaller range, however, at the stage of recruiting patients for the study, the age range had to be extended. Most of the respondents range from 30 and 55 age categories. Only three people are under 30 and eleven men with alcohol use disorder are between 56 and 59 years of age. Additional research constraints is the clinical status of the study group, the members of which had other, less significant, factors affecting their health. Another constraint of the scope of conclusions drawn from the study is the number of people in particular groups depending on the efficiency of memory processes. Most people are characterized by visuospatial memory disorders, while only 10 people have both auditory-verbal memory disorders and normal visuospatial memory. This is a small group, so the conclusions should be confirmed by a research in a bigger patient population. Despite the fact that memory disorders are often present in people with alcohol use disorder, less studies focused on the comparison of two groups of patients with visuospatial and auditory-verbal memory disorders. In neuropsychological diagnosis and therapy, it is key what type of memory is impaired. Another constraint is a wide range of abstinence times. However, only two people reported very long periods of abstinence exceeding 100 days and it is possible, that in the context of the brain structural change assessment, the vascularization process will not have a significant impact on the corpus callosum atrophy in the patient group under study. Moreover, in spite of the detailed MRI analysis and the demonstrated lack of statistically significant differences between the total corpus callosum area (the length and subregions) from the 1.5 T and 3 T scanners, additionally the analysis was carried out by using only 3T MRI data. Further research seems to be needed in order to reach more certain conclusions regarding the impact of consumption variables and other brain structural changes concerning the memory and attention processes of men with alcohol use disorder.

6. Conclusions

Our major conclusions are as follows. Visuospatial memory disorders often occurred in patients with lower lev-

els of education, longer history of alcohol abuse, higher daily alcohol consumption, and higher severity of alcohol use disorder. Additionally, we observed a smaller cross-sectional area of the total corpus callosum and its four subregions (genu, anterior mid-body, posterior mid-body, and splenium) in the population of alcohol-dependent men with both nonverbal and verbal memory disorders. Moreover, the alcohol abuse duration was a clinical significance in predicting the rostral body atrophy of the corpus callosum, only in alcohol-dependent men with disordered memory (auditory-verbal and visuospatial). Among the individuals with normal memory it was observed that the older age was a significant predictor of the smaller rostral body of the corpus callosum. On the other hand, the lower learning efficiency of visuospatial memory was significantly associated with callosal genu and isthmus atrophy in all alcohol-dependent men. To sum up, the genu area of the corpus callosum plays a crucial role in the neuropsychological profile, especially for visual attention, memory capacity (mainly in learning efficiency of visual modality), and memory disorder (auditory-verbal and visuospatial). We also observed a significant role of the elderly age, that is associated with corpus callosum atrophy and cognitive disorders.

Abbreviations

AVM, Auditory-Verbal Memory; VSM, Visuospatial Memory; LDCR, Long Delayed Cued Recall; LDFR, Long Delayed Free Recall; SDCR, Short Delayed Cued Recall; SDFR, Short Delayed Free Recall.

Availability of Data and Materials

Data was deposited in a available repository in the OSF | Corpus Callosum Atrophy in AUD.

Author Contributions

NN conceptualized and designed the study, performed the research, delivered the MRI analysis, analyzed the data, wrote the manuscript; MM delivered the MRI analysis; LC conceptualized and designed the study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All procedures performed in this study involving alcohol-dependent men were in accordance with the ethical standards of Faculty of Psychology and Cognitive Science at Adam Mickiewicz Univeristy of Ethics Committee for Research Projects (number 8/03/07/2018). All subjects gave written informed consent before their enrolment into the study.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] George MRM, Potts G, Kothman D, Martin L, Mukundan CR. Frontal deficits in alcoholism: an ERP study. Brain and Cognition. 2004; 54: 245–247.

[2] Bullock K, Cservenka A, Ray LA. Severity of alcohol dependence is negatively related to hypothalamic and prefrontal cortical gray matter density in heavy drinking smokers. The American Journal of Drug and Alcohol Abuse. 2017; 43: 281–290.

[3] Vanderhasselt M, Allaert J, De Raedt R, Baeken C, Krebs RM, Herremans S. Bifrontal tDCS applied to the dorsolateral prefrontal cortex in heavy drinkers: Influence on reward-triggered approach bias and alcohol consumption. Brain and Cognition. 2020; 138: 105512.

[4] Fama R, Le Berre A, Sassoon SA, Zahr NM, Pohl KM, Pfefferbaum A, *et al*. Relations between cognitive and motor deficits and regional brain volumes in individuals with alcoholism. Brain Structure & Function. 2019; 224: 2087–2101.

[5] Lee S, Jung Y, Na DL, Park SH, Kim M. Corpus callosum atrophy in Wernicke's encephalopathy. Journal of Neuroimaging: Official Journal of the American Society of Neuroimaging. 2005; 15: 367–372.

[6] Pitel A, Chételat G, Le Berre AP, Desgranges B, Eustache F, Beaunieux H. Macrostructural abnormalities in Korsakoff syndrome compared with uncomplicated alcoholism. Neurology. 2012; 78: 1330–1333.

[7] Pontes CM, Cagy M, Santos R, Soares CN. The importance of brain MRI in the diagnosis of Marchiafava-Bignami disease. Journal of Neurological Disorders. 2017; 3: 201–205.

[8] Zahr NM, Pfefferbaum A. Alcohol's Effects on the Brain: Neuroimaging Results in Humans and Animal Models. Alcohol Research: Current Reviews. 2017; 38: 183–206.

[9] Friedrich P, Fraenz C, Schlüter C, Ocklenburg S, Mädler B, Güntürkün O, *et al*. The Relationship Between Axon Density, Myelination, and Fractional Anisotropy in the Human Corpus Callosum. Cerebral Cortex (New York, N.Y.: 1991). 2020; 30: 2042–2056.

[10] Orrison WW. Atlas of Brain Function. Thieme: New York, USA. 2008.

[11] de Souza RSM, Rosa M, Escobar TDC, Gasparetto EL, Nakamura-Palacios EM. Anterior to Midposterior Corpus Callosum Subregions Are Volumetrically Reduced in Male Alcoholics but Only the Anterior Segment Is Associated to Alcohol Use. Frontiers in Psychiatry. 2019; 10: 196.
[12] Ruiz SM, Oscar-Berman M, Sawyer KS, Valmas MM, Urban T, Harris GJ. Drinking history associations with regional white matter volumes in alcoholic men and women. Alcoholism, Clinical and Experimental Research. 2013; 37: 110–122.
[13] Pfefferbaum A, Lim KO, Desmond JE, Sullivan EV. Thinning of the corpus callosum in older alcoholic men: a magnetic resonance imaging study. Alcoholism, Clinical and Experimental Research. 1996; 20: 752–757.
[14] Venkatasubramanian G, Anthony G, Reddy US, Reddy VV, Jayakumar PN, Benegal V. Corpus callosum abnormalities associated with greater externalizing behaviors in subjects at high risk for alcohol dependence. Psychiatry Research. 2007; 156: 209–215.
[15] Nowaczyk N. Frontal and callosal white matter changes and their potential effects on neurocognitive functioning in alcohol addicts: A meta-analysis. Acta Neuropsychologica. 2019; 17: 189–205.
[16] Nowaczyk N. Zmiany strukturalne mózgu a obraz kliniczny funkcji neuropsychologicznych u mężczyzn z zaburzeniem używania alkoholu [Structural changes in the brain and the clinical image of neuropsychological functions in men with alcohol use disorders]. Unpublished doctoral dissertation at Adam Mickiewicz University. Faculty of Psychology and Cognitive Science: Poznan, Poland. 2021.
[17] Mulhauser K, Weinstock J, Ruppert P, Benware J. Changes in Neuropsychological Status during the Initial Phase of Abstinence in Alcohol Use Disorder: Neurocognitive Impairment and Implications for Clinical Care. Substance Use & Misuse. 2018; 53: 881–890.
[18] Ioime L, Guglielmo R, Affini GF, Quatrale M, Martinotti G, Callea A, *et al*. Neuropsychological Performance in Alcohol Dependent Patients: A One-Year Longitudinal Study. Psychiatry Investigation. 2018; 15: 505–513.
[19] Paikkatt B, Akhouri S, Jahan M, Singh AR. Visuospatial constructional ability, visual memory and recognition ability among individuals with chronic alcohol dependence on the Rey complex figure test (RCFT). Acta Neuropsychologica. 2014; 12: 319–328.
[20] Stavro K, Pelletier J, Potvin S. Widespread and sustained cognitive deficits in alcoholism: a meta-analysis. Addiction Biology. 2013; 18: 203–213.
[21] Brion M, Pitel A, Beaunieux H, Maurage P. Revisiting the continuum hypothesis: toward an in-depth exploration of executive functions in korsakoff syndrome. Frontiers in Human Neuroscience. 2014; 8: 498.
[22] Pandey AK, Kamarajan C, Tang Y, Chorlian DB, Roopesh BN, Manz N, *et al*. Neurocognitive deficits in male alcoholics: an ERP/sLORETA analysis of the N2 component in an equal probability Go/NoGo task. Biological Psychology. 2012; 89: 170–182.
[23] Virag M, Janacsek K, Horvath A, Bujdoso Z, Fabo D, Nemeth D. Competition between frontal lobe functions and implicit sequence learning: evidence from the long-term effects of alcohol. Experimental Brain Research. 2015; 233: 2081–2089.
[24] Cierpiałkowska L, Ziarko M. Psychology of addictions: Alcoholism. WSiP: Warsaw, Poland. 2010. (In Polish)
[25] Nowakowska K, Jabłkowska K, Borkowska A. Cognitive dysfunctions in patients with alcohol dependence. Psychiatria Polska. 2007; 41: 693–702.
[26] Schulte T, Pfefferbaum A, Sullivan EV. Parallel interhemispheric processing in aging and alcoholism: relation to corpus callosum size. Neuropsychologia. 2004; 42: 257–271.
[27] Schulte T, Müller-Oehring EM, Salo R, Pfefferbaum A, Sullivan EV. Callosal involvement in a lateralized stroop task in alcoholic and healthy subjects. Neuropsychology. 2006; 20: 727–736.
[28] Bau CH, Spode A, Ponso AC, Elias EP, Garcia CE, Costa FT, *et al*. Heterogeneity in early onset alcoholism suggests a third group of alcoholics. Alcohol (Fayetteville, N.Y.). 2001; 23: 9–13.
[29] Alfonso-Loeches S, Pascual M, Guerri C. Gender differences in alcohol-induced neurotoxicity and brain damage. Toxicology. 2013; 311: 27–34.
[30] Nair V, Verma T, Yadav D, Lall SB. Cognitive failures among young male alcoholics compared across levels of alcoholism. Indian Journal of Health & Wellbeing. 2017; 8: 1505–1509.
[31] Schulte T, Sullivan EV, Müller-Oehring EM, Adalsteinsson E, Pfefferbaum A. Corpus callosal microstructural integrity influences interhemispheric processing: a diffusion tensor imaging study. Cerebral Cortex (New York, N.Y.: 1991). 2005; 15: 1384–1392.
[32] Gao L, Yang Y, Cai L, Xiong Y. Gender Differences in Pain Subtypes among Patients with Parkinson's Disease. Journal of Integrative Neuroscience. 2022; 21: 120.
[33] Pappas J. Cognitive Deficits and Changes in Ethanol Intake in Offspring of Male Alcoholics. ProQuest, Southern Connecticut State University: New Haven, USA. 2017.
[34] Sullivan EV, Fama R, Rosenbloom MJ, Pfefferbaum A. A profile of neuropsychological deficits in alcoholic women. Neuropsychology. 2002; 16: 74–83.
[35] Selzer ML. The Michigan alcoholism screening test: the quest for a new diagnostic instrument. The American Journal of Psychiatry. 1971; 127: 1653–1658.
[36] Falicki Z, Karczewski J, Wandzel L, Chrzanowski W. Usefulness of the Michigan Alcoholism Screening Test (MAST) in Poland. Psychiatria Polska. 1986; 20: 38–42.
[37] Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test Manual. Harcourt Brace Jovanovich: San Diego, USA. 1987.
[38] Łojek E, Stańczak J. Podręcznik do Kalifornijskiego testu uczenia się językowego: Polska normalizacja. Pracownia Testów Psychologicznych Polskiego Towarzystwa Psychologicznego: Warsaw, Poland. 2010. (In Polish)
[39] Donders J. A confirmatory factor analysis of the California Verbal Learning Test–Second Edition (CVLT-II) in the standardization sample. Assessment. 2008; 15: 123–131.
[40] Weidlich S, Lamberti G, Dajek E. DUM. Diagnosis of brain damage of F. Hillers. Erda: Warsaw, Poland. 2012. (In Polish)
[41] Weidlich S, Lamberti G. DCS: Diagnosticum für Cerebralschädigung nach F. Hillers. Verlag Hans Huber: Berno, Szwajcaria. 1997. (In Polish)
[42] Dajek ER. Polish standardization of d2 test, Attention test of R. Brickenkamp. Erda: Warsaw, Poland. 2012. (In Polish)
[43] Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, *et al*. Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage. 2004; 23 Suppl 1: S208–19.
[44] Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. IEEE Transactions on Medical Imaging. 2001; 20: 45–57.
[45] Smith SM. Fast robust automated brain extraction. Human Brain Mapping. 2002; 17: 143–155.
[46] Ardekani BA. Yuki module of the Automatic Registration Toolbox (ART) for corpus callosum segmentation. 2013. Available at: https://www.nitrc.org/projects/art (Accessed: 15 August 2022).
[47] Witelson SF. Hand and sex differences in the isthmus and genu of

the human corpus callosum. A postmortem morphological study. Brain. 1989; 112 (Pt 3): 799–835.
[48] Friederici AD, von Cramon DY, Kotz SA. Role of the corpus callosum in speech comprehension: interfacing syntax and prosody. Neuron. 2007; 53: 135–145.
[49] Guz W, Pazdan D, Stachyra S, Świętoń F, Poręba P, Bednarz M, *et al*. Analysis of corpus callosum size depending on age and sex. Folia Morphologica. 2019; 78: 24–32.
[50] Pfefferbaum A, Adalsteinsson E, Sullivan EV. Dysmorphology and microstructural degradation of the corpus callosum: Interaction of age and alcoholism. Neurobiology of Aging. 2006; 27: 994–1009.
[51] Pop-Jordanova N, Demerdzieva A. How Alcohol Damages Brain Development in Children. Prilozi (Makedonska Akademija Na Naukite i Umetnostite. Oddelenie Za Medicinski Nauki). 2022; 43: 29–42.
[52] Chandran S, Sreeraj VS, Venkatasubramanian G, Sathyaprabha TN, Murthy P. Corpus callosum morphometry in children with prenatal alcohol exposure. Psychiatry Research. Neuroimaging. 2021; 318: 111405.
[53] Moore EM, Xia Y. Neurodevelopmental Trajectories Following Prenatal Alcohol Exposure. Frontiers in Human Neuroscience. 2022; 15: 695855.
[54] Bookstein FL, Sampson PD, Streissguth AP, Connor PD. Geometric morphometrics of corpus callosum and subcortical structures in the fetal-alcohol-affected brain. Teratology. 2001; 64: 4–32.
[55] Wozniak JR, Muetzel RL, Mueller BA, McGee CL, Freerks MA, Ward EE, *et al*. Microstructural corpus callosum anomalies in children with prenatal alcohol exposure: an extension of previous diffusion tensor imaging findings. Alcoholism, Clinical and Experimental Research. 2009; 33: 1825–1835.
[56] Inkelis SM, Moore EM, Bischoff-Grethe A, Riley EP. Neurodevelopment in adolescents and adults with fetal alcohol spectrum disorders (FASD): A magnetic resonance region of interest analysis. Brain Research. 2020; 1732: 146654.
[57] Tian TY, Pescador Ruschel MA, Park S, Liang JW. Marchiafava Bignami Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2022. Available at: http://www.ncbi.nlm.nih.gov/books/NBK526007/ (Accessed: 29 December 2022).
[58] Wozniak JR, Riley EP, Charness ME. Clinical presentation, diagnosis, and management of fetal alcohol spectrum disorder. The Lancet. Neurology. 2019; 18: 760–770.
[59] Hemingway SJA, Davies JK, Jirikowic T, Olson EM. What proportion of the brain structural and functional abnormalities observed among children with fetal alcohol spectrum disorder is explained by their prenatal alcohol exposure and their other prenatal and postnatal risks? Advances in Pediatric Research. 2020; 7: 41.
[60] Holla B, Bharath RD, Venkatasubramanian G, Benegal V. Altered brain cortical maturation is found in adolescents with a family history of alcoholism. Addiction Biology. 2019; 24: 835–845.
[61] Kumar R, Kumar KJ, Benegal V. Cognitive and behavioural dispositions in offspring at high risk for alcoholism. Asian Journal of Psychiatry. 2018; 35: 38–44.
[62] Bookstein FL, Streissguth AP, Sampson PD, Connor PD, Barr HM. Corpus callosum shape and neuropsychological deficits in adult males with heavy fetal alcohol exposure. NeuroImage. 2002; 15: 233–251.
[63] Kelly DA, Seidenberg M, Reiter K, Nielson KA, Woodard JL, Smith JC, *et al*. Differential 5-year brain atrophy rates in cognitively declining and stable APOE-ε4 elders. Neuropsychology. 2018; 32: 647–653.
[64] Spitta G, Fliedner LE, Gleich T, Zindler T, Sebold M, Buchert R, *et al*. Association between DRD2/ANKK1 TaqIA Allele Status and Striatal Dopamine D2/3 Receptor Availability in Alcohol Use Disorder. Journal of Integrative Neuroscience. 2022; 21: 171.
[65] Erickson RL, Paul LK, Brown WS. Verbal learning and memory in agenesis of the corpus callosum. Neuropsychologia. 2014; 60: 121–130.
[66] Zehra A, Lindgren E, Wiers CE, Freeman C, Miller G, Ramirez V, *et al*. Neural correlates of visual attention in alcohol use disorder. Drug and Alcohol Dependence. 2019; 194: 430–437.
[67] Grossberg S. Attention: Multiple types, brain resonances, psychological functions, and conscious states. Journal of Integrative Neuroscience. 2021; 20: 197–232.
[68] Nikolakaros G, Kurki T, Myllymäki A, Ilonen T. A patient with Korsakoff syndrome of psychiatric and alcoholic etiology presenting as DSM-5 mild neurocognitive disorder. Neuropsychiatric Disease and Treatment. 2019; 15: 1311–1320.
[69] Hildebrandt H, Brokate B, Eling P, Lanz M. Response shifting and inhibition, but not working memory, are impaired after long-term heavy alcohol consumption. Neuropsychology. 2004; 18: 203–211.