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Structural brain substrates of the deficits observed on the BEARNI test in Alcohol Use Disorder and Korsakoff's syndrome

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Abstract

Chronic and excessive alcohol consumption can result in Alcohol Use Disorder (AUD) without neurological complications and in Korsakoff's syndrome (KS) when combined with thiamine deficiency. These two clinical forms are accompanied by widespread structural brain damage in both the fronto-cerebellar (FCC) and Papez circuits (PC) as well as in the parietal cortex, resulting in cognitive and motor deficits. BEARNI is a screening tool especially designed to detect neuropsychological impairments in AUD. However, the sensitivity of this tool to the structural brain damage of AUD and KS patients remains unknown.

Eighteen KS patients, 47 AUD patients and 27 healthy controls (HC) underwent the BEARNI test and a 3T-MRI examination. Multiple regression analyses conducted between GM density and performance on each BEARNI subtest revealed correlations with regions included in the FCC, PC, thalamus and posterior cortex (precuneus and calcarine regions). All these brain regions were altered in KS compared to HC, in agreement with the cognitive deficits observed in the corresponding BEARNI subtests. The comparison between KS and AUD regarding the GM density in the several nodes of the FCC and calcarine regions revealed that they were atrophied to the same extent, suggesting that BEARNI is sensitive to the severity of alcohol-related GM abnormalities. Within the PC, the density of the cingulate cortex and thalamus, which correlated with the memory and fluency subscores, was smaller in KS than in AUD, suggesting that BEARNI is sensitive to specific brain abnormalities occurring in KS.

Key words: BEARNI, alcohol use disorder, Korsakoff's syndrome, neuropsychological screening, brain damage

Significance statement

BEARNI is a screening tool especially design to assess motor and cognitive deficits in alcohol use disorder (AUD). Neuroimaging analyses conducted in AUD and Korsakoff's (KS) patients between BEARNI performance on the subtests and grey matter (GM) density reveal relationships with specific brain regions: the fronto-cerebellar and Papez circuits, thalamus, precuneus and calcarine regions. The comparisons of regional GM density show either that they were atrophied to the same extent in the two patient groups or a graded effect of density deficits between AUD and KS. These findings suggest that BEARNI is sensitive to alcohol-related brain structural abnormalities.

1. Introduction

Alcohol Use Disorder (AUD), even in absence of neurological complications such as Korsakoff's syndrome (KS), is associated with widespread structural brain damage (Gilman et al., 1990; Pitel et al., 2012; Ritz et al., 2015b; Sullivan, 2003). Previous studies showed alcohol-related grey matter (GM) volume deficits predominantly in the frontal cortices (Chanraud et al., 2007; Pitel et al., 2012), cerebellum (Chanraud et al., 2007) and cerebellar vermis (Sullivan et al., 2009). In addition, chronic and excessive alcohol consumption results in shrinkage of the thalamus (Chanraud et al., 2007; Pitel et al., 2012; Sullivan, 2003), cingulate cortex (Chanraud et al., 2007; Pitel et al., 2012), hippocampus (Sullivan et al., 1995) and mammillary bodies (Sullivan et al., 1999). Most of those regions are nodes of two brain networks that are thus especially affected in AUD: the fronto-cerebellar circuit (FCC) and the Papez's circuit (PC). The parietal cortex was also repeatedly found to be atrophied in AUD patients (Cardenas et al., 2007; Chanraud et al., 2007; Pitel et al., 2012; Ritz et al., 2015b).

KS results from the combination of heavy alcohol consumption and thiamine deficiency and is mainly characterized by persistent amnesia (Kopelman, 1995; Kopelman et al., 2009). Comparisons between AUD patients with and without KS revealed similarities in the regional distribution of GM abnormalities (Pitel et al., 2012) with the FCC being affected to the same extent in AUD and KS patients. However, the PC (especially the thalamus) was more severely damaged in KS than AUD patients. The severity of the structural brain damage within the PC would thus enable the distinction between KS and AUD patients (Pitel et al., 2015).

In clinical settings, AUD patients are rarely examined with an MRI because a neuroimaging investigation is costly, not easily obtainable and not sufficient for the distinction between AUD and KS. The diagnosis of KS requires indeed an extensive neuropsychological examination including the assessment of specific cognitive functions and a follow-up evaluation to ascertain the persistence of severe memory impairments. However, few addiction departments have the

financial resources and qualified clinical staff needed to administer such an extensive neuropsychological examination. Thus, a rapid screening is essential to identify patients who should be referred to a psychologist for a comprehensive neuropsychological evaluation.

Brief Evaluation of Alcohol-Related Neuropsychological Impairments (BEARNI) task is a validated screening tool especially designed to detect alcohol-related neuropsychological impairments (Pelletier et al., 2018; Ritz et al., 2015a). It was found to be a reliable predictor of performance on an extensive neuropsychological battery (Ritz et al., 2015) and relevant in the cognitive screening of AUD and KS patients (Ritz et al., 2021). AUD patients with a low episodic memory score on BEARNI were considered at risk of developing KS (Ritz et al., 2021), suggesting that BEARNI may make possible the early identification of AUD patients at high risk of developing KS. However, the relationships between performance on BEARNI and structural abnormalities in AUD and KS patients remain unknown. The goal of the present investigation is thus to strengthen the validation of BEARNI as a relevant screening tool in AUD and KS by identifying the specific brain regions whose volumes are related to cognitive and motor performance on BEARNI.

2. Material and Methods

2.1. Participants

All participants were included in a previous study (Ritz et al., 2021): 18 KS patients, 47 AUD patients and 27 healthy controls (HC) (Table 1). KS patients were diagnosed with reference to the clinical DSM-IV criteria of “amnesia due to substance abuse” and to the DSM-5 criteria of “major neurocognitive disorders, confabulatory type, persistent”. AUD patients were recruited by clinicians according to the DSM 5 criteria for AUD while they were receiving alcohol treatment in hospital. AUD patients were interviewed with the Alcohol Use Disorders Identification Test (AUDIT; (Gache et al., 2005)), and questions accompanying the Structured

Clinical Interview for DSM-IV-TR (SCID; (First and Gibbon, 2004)) with measures regarding the duration of alcohol misuse (in years), number of detoxifications (including the current one) and daily alcohol consumption over the month prior treatment (in units, a standard drink corresponding to a beverage containing 10 g of pure alcohol) (Table 1). All KS patients had a history of heavy drinking, but it was difficult to obtain accurate information about their alcohol intake due to their amnesia.

HC did not meet the DSM-5 for alcohol use disorder, did not meet the DSM-IV criteria for alcohol abuse or dependence (AUDIT < 7 for men and < 6 for women; (Gache et al., 2005)) and none of them had neuropsychological impairments on an extensive neuropsychological battery (data not shown).

All participants were informed about the study approved by the local ethics committee of the Caen University Hospital (CPP Nord Ouest III n° IDRCB: 2011-A00495) prior to their inclusion and provided their written informed consents.

Since KS patients were older and less educated than both HC and AUD participants. Age and education were thus included as covariates in the statistical analyses. Gender was also used as a covariate because of difference regarding sex ratio in the KS group (Table 1).

2.2. Neuropsychological screening with BEARNI

All participants underwent the BEARNI (Ritz et al., 2015a).

The *episodic memory* subtest consists of two learning trials of a 12-word list (4 words x 3 semantic categories). After a 20-minute interval (after the rest of the BEARNI has been administered), delayed free recall is performed (one trial lasting 1 minute). The episodic measure is the number of correct responses (0.5 point per response) minus the number of errors (intrusions and perseverations; 0.5 point per error) during the delayed free recall task (maximum score: 6 points).

Working memory is assessed with an alphabetical span subtest. Increasingly long letter sequences are read out loud, and for each sequence the patient has to repeat the letters in alphabetical order. Two trials are performed for each sequence. The task ends when the participant fails both two trials of a sequence (0.5 point per trial; maximum score: 5 points).

Executive functions are assessed with the alternating verbal fluency subtest (120 seconds to generate as many words as possible from two alternating categories (“color name” and “city name”). Depending on the number of correct responses, points range from 0 to 6.

Visuospatial abilities are assessed a subtest including five complex figures, each containing two separate hidden figures that the patient has to find. For each complex figure, one point is provided when the patient finds both hidden figures within 1 minute (maximum score: 5 points).

Finally, the *ataxia* subtest requires patients to stand on each foot in turn for 30 seconds, first with eyes open, then with eyes closed. There are up to two trials per condition. For each condition, 2 points are awarded when patients successfully perform the task at the first trial, 1 point when they successfully perform the task at the second trial, and 0 point when they fail both trials (maximum score: 8 points).

BEARNI provides six scores: five sub-scores (one for each of the subtests) and a total score (maximum score: 30 points). Raw scores on BEARNI are provided in table 2.

In the previous study using BEARNI and conducted in AUD and KS (Ritz et al., 2021), comparisons between KS, AUD patients and HC revealed that for all BEARNI subtests, KS patients had lower performance than HC. KS patients also performed lower than AUD patients for the episodic memory, executive and visuospatial subtests. In AUD patients, working memory, visuospatial and ataxia subtests were impaired compared to HC.

2.3. Magnetic resonance imaging

Each participant also underwent 3T MRI examination within the same week as the BEARNI test.

Acquisition and pre-processing of MRI data

For each participant, a high-resolution T1-weighted anatomical image was acquired on a Philips Achieva 3T scanner using a three-dimensional fast-field echo sequence (sagittal; repetition time, 20 ms; echo time, 4.6 ms; flip angle, 10°; 180 slices; slice thickness, 1 mm; field of view, 256 x 256 mm²; matrix, 256 x 256).

The volumetric MRI data were analyzed using the Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Pre-processing steps included segmentation of the MRI data into gray matter (GM) white matter (WM) and cerebrospinal fluid (CSF) and spatial normalization to the Montreal Neurological Institute (MNI) template (voxel size = 1.5mm³, matrix = 121 x 145 x 121). The normalized GM images were modulated by the Jacobian determinants to correct for non-linear warping only so that the resulting brain volumes were corrected for brain size. The resulting images were smoothed by a Gaussian kernel of 8 mm full-width-at-half-maximum (FWHM).

The mask of GM tissue was obtained by averaging the GM images in MNI space of the control subjects and setting all voxels where GM was greater than both WM and CSF to 1 (i.e. $(GM > WM) \cap (GM > CSF) = 1$). The resulting binary GM mask was applied to the MRI data sets.

2.4. Statistical analyses

Multiple regressions between BEARNI performance and MRI data in AUD and KS

For each participant and each BEARNI subtest, performance was transformed into z-scores based on the mean and standard deviation of the HC. This linear transformation to standard normal distribution allows to maintain the same statistical distribution and to directly compare each BEARNI subtest performance in the three groups of participants (HC, AUD and KS), as

previously performed in (Ritz et al., 2021) and classically used in clinical practice to analyze results in patients.

For each subtest, voxel-based multiple regressions (without age, sex and education in covariates) were then conducted between BEARNI performance and GM density in KS and AUD patients pooled together. Increased variability in GM density in a brain region can exist for several reasons other than the direct effect of the neurotoxicity of alcohol consumption. It could be the secondary effect from another brain region which has been directly damaged. It could also reflect a pre-morbid scenario for AUD or addiction in general. Regarding the main objective of the present study, specific to AUD patients, healthy controls were not included in this analysis. We used SPM12 with a p value < 0.001 (uncorrected at the peak level but corrected for multiple comparisons at the cluster-level, $p < 0.05$; a stringent statistical threshold to prevent type I error) and an extent threshold of $k = 200$ voxels (corresponding to 675mm^3). For a smooth at 8mm, the min cluster size is 512 mm^3 (8^3). We have chosen a cluster size of 675 mm^3 so that the regions are big enough in size to avoid results due to noise or partial volumes between GM and WM or CSF. Nevertheless, we have kept the cluster size small enough to detect significant differences in relatively smaller regions like the hippocampus and the thalamus.

GM anatomical localization was carried out using automated anatomical labeling software (Tzourio-Mazoyer et al., 2002) and verified using the Harvard-Oxford cortical and subcortical structural atlases implemented in FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fsl4.0/fslview/atlas-descriptions.html#ho>).

Comparisons of GM density in the three groups

We then extracted the GM density within each significant cluster resulting from the multiple regression analyses described above (corresponding to the sum of GM volume at the cluster

level in mm³/ number of voxels of the cluster). This scaling in mm³/voxel allows to directly compare clusters between them. GM density of each significant cluster was then compared with Statistica software in the three groups using MANCOVAs (three groups (HC, AUD and KS) clusters, with age, sex and education as covariates) followed by post-hoc comparisons (Tukey's tests). HC were included in this analysis to compare, a posteriori, the GM density of the significant cluster correlated with BEARNI performance, to assess the differences between HC and KS, HC and AUD and AUD and KS and thus to statute on the level and severity of GM atrophy in AUD patients. The rationale to distinguish AUD from KS is to determine whether the phenomena we observe are either a graded effect (HC > AUD > KS) that is most probably due to a prolonged exposure to alcohol consumption, or specific to KS only, which would imply pathophysiological mechanisms beyond the sole direct neurotoxic effect of alcohol on the brain. We only reported results showing a significant group * cluster interaction effect at $p \leq 0.050$. Findings of the interaction group * cluster allow to determine whether GM density of some clusters show distinct profile between HC, AUD and KS. When the interaction was not significant, the main effect of group was reported. Effect size (partial eta square) was reported (<0.06: small effect size; 0.06 to 0.14: moderate effect size; >0.14: large effect size). The normality of each distribution was assessed with the Shapiro-Wilk Test.

3. Results

3.1. Structural brain substrates of BEARNI performance in the two groups of patients

Results are depicted in figure 1. Multiple regressions conducted between GM density and results on the BEARNI *episodic memory subtest* in AUD and KS patients pooled together revealed significant correlations with the middle cingulate cortex (cluster size 3169 voxels; 6166 mm³), superior frontal gyrus (BA 9) including supplementary motor area (BA 6; cluster size 1656 voxels; 5589 mm³) and thalamus (cluster size 271 voxels; 915 mm³).

Regarding the *fluency* subtest, significant correlations were found with the cingulate cortices (cluster size 1827 voxels; 6166 mm³), middle frontal gyrus (BA 9 and 46; cluster size 815 voxels; 2751 mm³), precentral gyrus (BA 6; cluster size 1015 voxels; 3426 mm³), cerebellum (vermis IV-V; cluster size 831 voxels; 2805 mm³) and parahippocampal gyrus (cluster size 562 voxels; 1897 mm³).

Performance on the *working memory* subtest of BEARNI revealed significant correlations with the posterior calcarine regions (cluster size 6442 voxels; 21742 mm³), precentral gyrus (BA 6; cluster size 345 voxels; 1164 mm³), thalamus (cluster size 539 voxels; 1819 mm³) and middle frontal gyrus (BA 46; cluster size 234 voxels; 790 mm³).

Regarding the *visuospatial* subtest, we found significant correlations with the precuneus (cluster size 3891 voxels; 13132 mm³), calcarine regions (cluster size 682 voxels; 2301 mm³), superior frontal gyrus (BA 9; cluster size 506 voxels; 1708 mm³) and cerebellum (lobules 4-5 as well as lobule 8; cluster size 900 voxels; 3037 mm³).

Finally, performance on the *ataxia* subtest revealed correlations with numerous regions of the fronto-cerebellar (cerebellum and frontal cortices) and Papez circuits (hippocampus and parahippocampal gyrus, cingulate cortex) as well as parietal cortices. Correlations with the precentral gyrus including supplementary motor area (BA 6; cluster size 2436 voxels; 8221 mm³), cerebellum (vermis IV-V and lobules 4-5; cluster size 370 voxels; 1249 mm³) and precuneus (cluster size 1853 voxels; 6254 mm³) remained significant when a more stringent threshold was applied (FWE p-corrected <0.05).

3.2. Comparisons of GM density in the three groups

Results of the MANCOVAs (three groups (HC, AUD and KS) * clusters, with age, sex and education as covariates) are reported in table 3. All of the data were normally distributed (Shapiro-Wilk tests >0.050).

Regarding the clusters of GM density that correlated with the *episodic memory* subscore of BEARNI, the MANCOVA did not reveal any significant interaction between group and cluster but a significant effect of group (with a large effect size). Tukey's post-hoc test showed that in the three clusters (middle cingulate cortex, superior frontal gyrus (BA 9) including supplementary motor area (BA 6) and thalamus), KS patients had lower GM density than both AUD patients and HC. AUD had lower GM density than HC (figures 2, 3 and 4).

For the clusters that significantly correlated with the *fluency* subscore, the MANCOVA revealed a significant interaction between the group and the cluster effects (with a moderate effect size). Tukey's post-hoc tests showed that for the cingulate cortex (figure 3B) and the precentral gyrus (BA 6; figure 2E), KS patients had lower GM density than AUD patients, who both presented shrinkage of these brain regions compared with HC. For the cerebellum (figure 2B) and parahippocampal gyrus (figure 3), both AUD and KS patients had lower GM density than HC but they did not differ between each other. For the middle frontal gyrus (figure 2H), KS had lower GM density than both AUD and HC, who did not differ between each other.

Concerning the *working memory* subscore of BEARNI, a significant interaction was found between the group and the cluster effects (with a large effect size). For the calcarine regions (figure 5D) and precentral gyrus (BA 6; figure 2F), both AUD and KS patients had lower GM density than HC but did not differ between each other. For the middle frontal gyrus (BA 46), AUD and KS patients had similar GM density (figure 2J). Contrary to AUD patients, KS patients had lower GM than HC. For the thalamus, KS patients had lower GM density than AUD patients, who both differed from HC (figure 4, right).

Regarding the clusters of GM density that correlated with the *visuospatial* subscore of BEARNI, the MANCOVA did not reveal any significant interaction between the group and cluster effects but a significant effect of group (with a large effect size). The Tukey's post-hoc test revealed that for the 5 clusters (precuneus, calcarine regions, superior frontal gyrus and

cerebellum (lobules 4-5 and 8), KS patients had lower GM density than both AUD patients and HC. There was a shrinkage of these regions in AUD compared with HC (figures 2C, 2I, 4A and 4C).

Finally, regarding the clusters of GM density that correlated with the *ataxia* subscore of BEARNI, the MANCOVA did not reveal any significant interaction between the group and cluster effect but a significant effect of group (with a large effect size). The Tukey's post-hoc test showed that KS patients had lower GM density in the precentral gyrus, cerebellum and precuneus than both AUD patients and HC. AUD had lower GM density than HC (figures 2A, 2D and 5B).

4. Discussion

BEARNI (Ritz et al., 2015a) is a validated screening cognitive tool especially designed to detect neuropsychological impairments in AUD. However, questions remain regarding its sensitivity to alcohol-related brain damage. In this study, cognitive and motor performance evaluated with subtests of BEARNI correlated with GM density of the PC, FCC, thalamus (shared region between these two brain circuits) as well as with the precuneus and calcarine regions. Interestingly, the total score computed as a sum of the scores collected on the subtests correlated with GM density of those regions (data not shown), reinforcing the relevance of this score to reflect alcohol-related brain abnormalities.

4.1. Fronto-cerebellar circuit (FCC)

Performance on all the BEARNI subtests correlated with GM density of the FCC nodes known to be involved in executive and motor functioning (Kelly and Strick, 2003; Zahr et al., 2010). Results on the ataxia subtest correlated with GM density of the motor loop of the FCC (premotor cortex (BA 6) and cerebellum (lobules 4-5 and vermis IV-V)). Comparisons of GM density in these brain regions revealed more severe shrinkage in KS than in AUD patients. The cerebellum

has been reported as more severely altered in KS and Wernicke's encephalopathy than in AUD patients (Harper et al., 2003; Sullivan and Pfefferbaum, 2009), potentially due to the associated severe nutritional (especially thiamine) deficiency (Harper, 2009; Maschke et al., 2005; Sullivan and Pfefferbaum, 2009). In accordance, the present results indicate that low results on the BEARNI ataxia subtest are related to cerebellum damage.

More surprisingly, performance on the cognitive subtests correlated not only with the frontal executive loop of the FCC (BA 9 and 46) but also with regional density of the motor loop nodes. These brain-behavior relationships suggest the contribution of executive functions in these subtests (for review see Pitel et al., 2014; Zahr et al., 2010) but also suggest the use of inefficient compensatory mechanisms involving the motor loop of the FCC (Chanraud et al., 2011, 2010). A more severe shrinkage of the superior frontal regions (BA 9) in KS compared with AUD is not in agreement with previous neuroimaging investigations showing similar structural abnormalities within the FCC in AUD and KS patients (Pitel et al., 2012). However, in our study, KS patients had more severe deficits than AUD in BEARNI subtests (episodic memory, fluency and visuospatial) that correlated with GM density of frontal cortices (Ritz et al., 2021). Several studies reported that in KS, cognitive impairments may be partially attributable to or exacerbated by frontal lobe alterations (for review see (Brion et al., 2014)). Conversely, AUD patients did not differ from KS regarding the severity of the GM density deficits in the middle frontal gyrus (BA 46), suggesting a common effect of chronic and excessive alcohol consumption on brain integrity.

4.2. Papez circuit (PC)

GM density of the PC nodes (more particularly the parahippocampal gyrus and cingulate cortex) correlated with performance on both the episodic memory and fluency subtests, suggesting that BEARNI is sensitive to alterations of memory network described in both AUD and KS patients (Chanraud et al., 2007; Pitel et al., 2012; Ritz et al., 2015b; Sullivan et al.,

1995). This finding is essential regarding the relevance of the BEARNI episodic memory subtest in the detection of AUD at high risk of developing KS (Ritz et al., 2021). In the present study, the cingulate cortex was more severely damaged in KS than in AUD. On the opposite, the parahippocampal gyrus was atrophied to the same extent in KS and AUD patients. Structural abnormalities within the PC could be the consequence of the severity and duration of alcohol consumption as well as the result of a nutritional (notably thiamine) deficiency. Relationship between thiamine deficiency and episodic memory deficits in AUD patients was previously reported (Pitel et al., 2011; Ritz et al., 2016). Thus, it is likely that AUD patients with poor performance on the fluency and episodic memory subtests of BEARNI, especially those with nutritional deficiency, present structural abnormalities within the PC, and notably in the parahippocampal gyrus and cingulate cortex.

4.3. Thalamus

GM density of the thalamus correlated with performance of both the episodic and working memory subtests. The thalamus is a key region of the PC and FCC and has connections with the mammillary bodies, cingulate gyrus and hippocampus on the one hand, and the cerebellum and frontal cortices on the other hand (for review see Pitel et al., 2014). The different thalamic nuclear groups are involved in specific cognitive abilities including episodic and working memory (Aggleton et al., 2011; Newsome et al., 2018; Pitel et al., 2014; Segobin et al., 2019; Segobin and Pitel, 2021). In the present study, as expected (Harding et al., 2000; Kopelman et al., 2009; Pitel et al., 2012), we found a graded effect of thalamic density deficits with more severe shrinkage in KS than in AUD. This result is in agreement with the poor episodic memory performance on BEARNI in KS compared with AUD and reinforces the relevance of this subtest in the detection of AUD at high risk of developing KS (Ritz et al., 2021). In a clinical point a view, AUD patients with severe deficits on the episodic and working memory subtests

of BEARNI may present severe atrophy of the thalamus and should thus benefit from particular attention.

4.4. Posterior regions

Finally, relationships were also found between GM density of the precuneus and calcarine regions and performance on the BEARNI subtests assessing working memory, visuospatial and motor functioning. These brain-behavior relationships could reflect the involvement of mental imagery (for review see Dijkstra et al., 2019), planning abilities and visual-motor integration (Teixeira et al., 2014) in these subtests. Either structural abnormalities were similar in KS and AUD patients (for the posterior calcarine regions), or a graded effect of density deficits was found between AUD and KS patients in the precuneus. These posterior regions were indeed repeatedly found to be atrophied in AUD and KS in the literature (Cardenas et al., 2007; Chanraud et al., 2007; Pitel et al., 2012; Ritz et al., 2015b). This finding suggests that BEARNI is sensitive to structural abnormalities occurring in brain posterior regions described as atrophied in AUD. Based on the effect size, the strong relationship between structural abnormalities in these posterior regions and the visuospatial deficits (as well as, to a lesser extent, working memory and motor deficits), highlights the relevance of examination of these cognitive functions in AUD.

4.5. Limitations

One of the limitations of the present study is that mainly men have been included, in accordance with the high proportion of men in Addiction department in France. Further studies including a higher proportion of women in the AUD group are required. The relationships between BEARNI performance and other neuroimaging modalities could also be investigated. The present investigation is cross-sectional. A follow-up study would enable to examine the concomitant changes in BEARNI performance and brain density depending of drinking status.

4.6. Conclusion

In AUD and KS patients, BEARNI performance correlated with GM density of the PC, FCC, thalamus as well as posterior regions. All these brain regions were altered in KS compared to HC, in agreement with the deficits observed in the BEARNI subtests (Ritz et al., 2021). The nodes of the PC and FCC, as well as the posterior regions, were atrophied either to the same extent in the two patient groups or showed a graded effect of density deficits between AUD and KS, suggesting that BEARNI is sensitive to alcohol-related GM abnormalities.

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Conflicts of interest

Authors declare no conflict of interest.

Author contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Writing the original draft: LR; methodology, formal analysis: SS; investigation: AL, CL, CB, FV, LU; funding acquisition: ALP; supervision, visualization, writing (review & editing): SS, ALP, HB

Data Availability Statement (DAS)

Data available on request from the authors: the data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1: Main features of the participants (drawn from (Ritz et al., 2021))

	KS patients N=18	AUD patients N=47	Healthy controls N=27	Statistical analyses
Men/Women	8/10	42/5	25/2	Chi ² =20.54; p<0.001 ¹
Age (years)	55.72 ± 5.49	46.91 ± 9.17	43.41 ± 6.29	F _(2,89) =13.84; p<0.001 ^{2*}
Range	44-67	26-66 ⁴	31-55	(HC=AUD)<KS
Education (years of schooling)	10.39 ± 2.52	11.83 ± 2.05	12.11 ± 1.69	F _(2,89) =4.22; p=0.017 ^{2*}
Range	6-15	9-17	9-15	(HC=AUD)>KS
AUDIT	-	28.65 ± 7.84	2.63 ± 1.60	F _(1,72) =380.10; p<0.001 ²
Range	-	9-39	0-6	AUD>HC
Days of sobriety before inclusion	-	11.89 ± 4.20	-	-
Range	-	4-24	-	-
Daily alcohol consumption during the month preceding treatment (units)	-	20.01 ± 8.68	-	-
Range	-	0-40	-	-
Duration of alcohol misuse (years)	-	22.87 ± 12.38	-	-
Range	-	5-46	-	-
Number of detoxifications	-	1.81 ± 1.52	-	-
Range	-	1-8	-	-

Data are shown as means ± standard deviations; -: data not applicable; KS: Korsakoff's syndrome; AUD: Alcohol Use Disorder; HC: healthy controls

¹ Chi² (correction of Yates applied)

* significant at p≤0.050

² One-way ANOVA (group): Tukey's post-hoc tests

³ ANCOVA (with age, sex and education as covariates), Tukey's post-hoc tests

⁴ Only one AUD patients had 65 years old and only 5 had more than 60 years old

Table 2: Performance (raw scores) on BEARNI (drawn from (Ritz et al., 2021))

BEARNI score	KS patients	AUD patients	Healthy controls
BEARNI total score	5.28 ± 2.48	13.78 ± 5.05	20.70 ± 2.30
<i>Range</i>	2-10.5	4-22.5	16.5-26
Episodic memory	0.22 ± 0.31	3.02 ± 1.40	3.55 ± 1.33
<i>Range</i>	0-1	0-5.5	1.5-5
Executive functions	2.22 ± 1.11	4.19 ± 1.15	4.93 ± 1.00
<i>Range</i>	0-4	2-6	2-6
Working memory	1.67 ± 0.80	2.39 ± 1.25	3.44 ± 0.92
<i>Range</i>	0-3.5	0-5	1.5-5
Visuospatial abilities	0.39 ± 0.61	1.78 ± 1.37	3.41 ± 1.08
<i>Range</i>	0-2	0-5	2-5
Ataxia	0.78 ± 1.40	2.38 ± 2.22	5.37 ± 1.77
<i>Range</i>	0-4	0-8	2-8

Data are shown as means ± standard deviations

KS: Korsakoff's syndrome: AUD: Alcohol Use Disorder

In the previous study (Ritz et al., 2021), comparisons between KS, AUD patients and HC revealed that for all BEARNI subtests, KS patients had lower performance than HC. KS patients also performed lower than AUD patients for the episodic memory, executive and visuospatial subtests. In AUD patients, working memory, visuospatial and ataxia subtests were impaired compared to HC.

Table 3: Comparisons of GM density in the significant clusters between the three groups of participants

Clusters	Interaction group * clusters of the MANCOVAs	Tukey's Post-hoc tests
<i>Significant clusters correlated with the episodic memory score of BEARNI</i>		
Middle cingulate cortex	ns interaction Significant effect of group: $F_{(2;84)} = 25.93; p < 0.001; \eta^2 = 0.38$	HC > AUD > KS
Superior frontal gyrus and SMA (BA 9 and 6)		
Thalamus		
<i>Significant clusters correlated with the fluency score of BEARNI</i>		
Cingulate cortex	Significant interaction: $F_{(8;340)} = 2.81; p = 0.050; \eta^2 = 0.09$	HC > AUD > KS
Middle frontal gyrus (BA 9)		HC = (AUD > KS)
Precentral gyrus (BA 6)		HC > AUD > KS
Cerebellum (vermis IV-V)		HC > (AUD = KS)
Parahippocampal gyrus		HC > (AUD = KS)
<i>Significant clusters correlated with the working memory score of BEARNI</i>		
Posterior calcarine regions	Significant interaction: $F_{(6;258)} = 13.98; p < 0.001; \eta^2 = 0.24$	HC > (AUD = KS)
Precentral gyrus (BA 6)		HC > (AUD = KS)
Thalamus		HC > AUD > KS
Middle frontal gyrus (BA 46)		HC = AUD; AUD = KS; HC > KS
<i>Significant clusters correlated with the visuospatial subtest of BEARNI</i>		
Precuneus	ns interaction Significant effect of group: $F_{(2;85)} = 18.30; p < 0.001; \eta^2 = 0.30$	HC > AUD > KS
Calcarine regions		
Superior frontal gyrus (BA 9)		
Cerebellum (lobules 4-5)		
Cerebellum (lobule 8)		
<i>Significant clusters correlated with the ataxia score of BEARNI</i>		
Precentral gyrus (BA 6)	ns interaction Significant effect of group: $F_{(2;84)} = 16.49; p < 0.001; \eta^2 = 0.30$	HC > AUD > KS
Cerebellum (vermis IV-V and lobules 4-5-6)		
Precuneus		

HC: Healthy controls; AUD: alcohol use disorder patients; KS: Korsakoff's patients

Results are shown as interaction resulting from MANCOVAs [3 groups (KS, AUD and HC) * significant clusters extracted from multiple regressions conducted between GM density and performances of each BEARNI subtest, with age, sex and education as covariates

SMA: supplementary motor area

ns : not significant ($p > 0.050$); η^2 = partial eta squared

Figure legends

Figure 1: Render on the MNI template of results from the regression analyses between performance on each BEARNI subtest and GM brain density in AUD and KS patients pooled together

Results are displayed at $p < 0.001$ (uncorrected at peak level but corrected for multiple comparisons at cluster-level, $p < 0.05$) except for ataxia (FWE p-corrected < 0.050). Render was performed by MRIcron software.

Figure 2: GM density (in mm^3/voxel) of the clusters included in the fronto-cerebellar circuit

ROIs at the top of the figure are atlas-based and used for displaying purposes of the anatomical localization of brain regions that were significant in the regression analysis. It is the significant clusters from the regression analysis that have been used for the subsequent statistical analyses

Cerebellar clusters density that significantly correlated with performance on BEARNI (A) ataxia; (B) executive and (C) visuospatial subtests

GM density of the motor frontal clusters that significantly correlated with performance on BEARNI (D) ataxia; (E) executive and working memory subtest (F).

GM density of the executive frontal clusters that significantly correlated with performance on BEARNI (G) episodic memory; (H) executive; (I) visuospatial and (J) working memory subtests.

HC: Healthy Controls; AUD: Alcohol Use Disorder; KS: Korsakoff's syndrome; WM: working memory

Pairwise difference with Tukey's post hoc. Significant difference at * $p \leq 0.050$; ** $p \leq 0.010$; *** $p \leq 0.001$

Figure 3: GM density (in mm^3/voxel) of the clusters included in the Papez circuit

ROIs at the top of the figure are atlas-based and used for displaying purposes of the anatomical localization of brain regions that were significant in the regression analysis. It is the significant clusters from the regression analysis that have been used for the subsequent statistical analyses

GM density of the cingulate clusters that significantly correlated with performance on BEARNI (A) episodic memory and (B) executive subtests

HC: Healthy Controls; AUD: Alcohol Use Disorder patients; KS: Korsakoff's syndrome patients; WM: working memory

Pairwise difference with Tukey's post hoc. Significant difference at * $p \leq 0.050$; ** $p \leq 0.010$; *** $p \leq 0.001$

Figure 4: GM density (in mm³/voxel) of the clusters included in the thalamus

ROIs at the top of the figure are atlas-based and used for displaying purposes of the anatomical localization of brain regions that were significant in the regression analysis. It is the significant clusters from the regression analysis that have been used for the subsequent statistical analyses

Thalamic clusters density that significantly correlated with performance on BEARNI episodic memory (to the left) and working memory (to the right)

HC: Healthy Controls; AUD: Alcohol Use Disorder patients; KS: Korsakoff's syndrome patients; WM: working memory

Pairwise difference with Tukey's post hoc. Significant difference at * $p \leq 0.050$; ** $p \leq 0.010$; *** $p \leq 0.001$

Figure 5: GM density (in mm³/voxel) of the posterior regions

ROIs at the top of the figure are atlas-based and used for displaying purposes of the anatomical localization of brain regions that were significant in the regression analysis. It is the significant clusters from the regression analysis that have been used for the subsequent statistical analyses

GM density of the precuneus clusters correlated with performance on BEARNI (A) visuospatial and (B) ataxia subtests

GM density of the calcarine clusters correlated with performance on BEARNI (C) visuospatial and (D) working memory subtests

HC: Healthy Controls; AUD: Alcohol Use Disorder patients; KS: Korsakoff's syndrome patients; WM: working memory

Pairwise difference with Tukey's post hoc. Significant difference at * $p \leq 0.050$; ** $p \leq 0.010$; *** $p \leq 0.001$