The relation of hippocampal subfield volumes to verbal episodic memory measured by the California Verbal Learning Test II in healthy adults.

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Abstract

Total hippocampal volume has previously been shown to correlate with performance on tests for verbal episodic memory. However, there are sparse evidence on how hippocampal subfield volumes are related to verbal episodic memory in healthy adults. The present study investigated the association between volumes of separate hippocampal subfields and verbal episodic memory performance in healthy volunteers. Forty-seven participants (31 females) between 20 to 71 years age underwent testing with the California Verbal Learning Test II (CVLT II), and the Wechsler Abbreviated Scale of Intelligence (WASI) to obtain an estimate of cognitive functioning. T1-weighted MR images were obtained after cognitive testing, and volumetric estimates adjusted for age and estimated total intracranial volume were calculated in the FreeSurfer 6.0 software suite for cerebral -and hippocampal structures. The sample performed within the statistical normal range on both CVLT II and WASI. Significant correlations adjusted for multiple testing were found between CVLT II subtests of total learning, free immediate recall and free delayed recall and volumes of the left Cornu Ammonis (CA) 1-4 subfields. There were no significant correlations between right hippocampal subfields and CVLT II performance, and no significant correlation between WASI results and hippocampal subfields. The present results suggest that better verbal episodic memory measured by the CVLT II is associated with relative larger volumes of specific left CA hippocampal subfields in healthy adults. Due to the small sample size and large age-span of the participants, the present findings are preliminary and should be confirmed in larger samples.

Keywords: Verbal memory; Hippocampal subfields; California Verbal Learning Test; FreeSurfer; Healthy Volunteers.

1. Introduction

Episodic memory, which is the ability to remember experiences that occurred at a particular place and time, has been related to hippocampal functions in several studies [1-3]. The hippocampus is usually subdivided into the Cornu Ammonis (CA) CA1, CA2-3, CA4/dentate gyrus, the presubiculum and the subiculum, which are the larger sub-structures of the hippocampus. Previous studies have suggested that these subfields have separate and specialized functions with regard to memory processes, and the subfield division are therefore not merely an anatomical classification [4, 5].

Development of advanced magnet resonance imaging (MRI) techniques during the last decades have provided the opportunity to study both anatomical features and cerebral activation with high precision. Volumetric MRI studies that combines structural assessment of the brain with concomitant cognitive measures provides the opportunity to study the inter-individual variability in brain structures that can be statistically related to certain categories of cognition [6]. The structural approach is useful when assessing whether structural individual differences in cerebral areas are associated with normal or impaired cognition [7].

The volume of the hippocampal subfields is assumed to be positively correlated with episodic memory functioning [8, 9], even if some studies have reported a negative association between hippocampal volume and memory processes [10, 11]. However, most previous volumetric studies of verbal memory and hippocampal size have used data for the hippocampus without separating the subfields and the number of studies investigating the relation between hippocampal subfields and cognitive functions are sparse. Furthermore, the results in the

existing studies are not entirely consistent, and differences in findings may arise from differences in characteristics of the samples, method for estimating hippocampal subfields and selection of cognitive tests.

A recent study using subfield segmentation of MRI data from healthy elderly showed that verbal memory performance measured by the Repeatable Battery for Assessment of Neuropsychological status (RBANS) shows that larger volumes of the CA1 and the subiculum were correlated with better verbal memory retrieval [12]. Another study on healthy younger adults using high-field MRI with manual hippocampal segmentation revealed that verbal memory performance [8] measured by the Wechsler Memory Scale III [13] was correlated with larger volumes of the CA1, CA2-3 and CA4. Using a measure for autobiographical episodic memory [14] in healthy young adults, Palombo et al., [15] found that volumes of the left CA2/3 and the bilateral subiculum were associated with higher number of details generated from an autobiographical interview. In case-control studies using the California Verbal Learning Test (CVLT-II) [16] to assess verbal memory, larger volumes of CA2-3 and CA4 were associated with better immediate verbal recall, whereas CA1 volume correlated with better delayed verbal recall [17, 18].

Early lesion studies indicated that verbal auditory memory is more dependent on the left hippocampus compared to the right [19], which have been supported in some more recent human volumetric studies [15, 20, 21]. Furthermore, several studies in healthy adults have found structural asymmetry with larger volumes of the right hippocampus compared to the left [22-24]. This asymmetry has also been shown to be associated with preserved memory functions in elderly persons, where memory impaired subjects had no significant volume asymmetry between the left and the right hippocampus [25]. The underlying mechanism for the structural asymmetry is unknown, but it may be related to the functional specialization of the temporal lobes, where the left side normally is more associated with verbal memory

whereas the right is associated with non-verbal memory functions [22, 26]. Thus, a lateralization effect of verbal episodic memory on hippocampal subfield volumes can be anticipated.

In the present study, we used the CVLT-II to assess verbal memory functions in healthy adults of both sexes in a wide age-span to test whether episodic verbal memory shows a lateralization effect in the hippocampus. The CVLT II is extensively used in both clinical and scientific settings [27], but there is limited data on the hippocampal anatomical correlates of CVLT II performance in healthy volunteers. Thus, data for structural correlates of the CVLT II is important for both clinical and scientific purposes. Based on findings in previous studies using similar methodology, we expected that different outcome measures of the CVLT-II had specific correlates of the hippocampal subfield volumes. Specifically, we hypothesized that the left CA2-3 and CA4 volumes should be associated with the learning score and immediate recall memory score, whereas the left CA1 and the subiculum should be associated with delayed recall performance.

2. Methods

2.1. Participants

Forty-seven, right-handed volunteers (31 females) in the age range 22 to 71 (Mean = 38.36, SD = 20.16) years were recruited on the campus of the University of Tromsø, Norway. The mean educational level of the sample was 13.78 (SD = 2.02) years (median = 14 years). All participants signed an informed consent stating that they were healthy and had no present or history of severe disease or injuries. The study was approved by the Regional Committee for Research Ethics in Medicine and Health Sciences (project 2012/1588) and was conducted

in accordance with the Declaration of Helsinki. The participants received a gift card worth 300 Norwegian Kroner (approx. 37 EUR/47 USD) as compensation for their participation. Exclusion criteria were previous concussions, traumatic brain injury, or other injuries or diseases involving the central nervous system, including psychiatric conditions. Patients on prescribed medications were excluded, with the exception of oral contraceptives in women. Medical conditions, pregnancy, or body implants not compatible with participants' safety in the MR-scanner were also exclusion criteria.

2.2. Neuropsychological tests

Verbal episodic memory was measured by the Norwegian version of the California Verbal Learning Test II (CVLT-II), standard version [16]. The CVLT-II measures verbal auditory learning, recall- and recognition memory, and was administrated and scored according to the standardized instructions. The learning trial gives a total score from five separate recalls of a 16-item word list (List A) that is read aloud to the examinee who is to repeat the words from the list in random order after each reading. Thereafter, a second list (List B) is introduced as a distractor before the examinee is asked to recall as many items as possible from List A. The correct items remembered from A after the distractor list, comprises the Immediate recall trial. Then, the examiner asks the participant to categorize the word list into four categories (i.e., furniture, vegetables, clothes, and animals) to obtain a measure of Immediate cued-recall abilities. Twenty minutes after the total learning trial, the free and cued recall of List A are repeated, and comprise the delayed recall trial and the delayed cued recall trial, respectively. At last a recognition trial and a forced recognition trial is performed.

The results from the cued recall trials were not included in the present data analyses due to high correlations with the free recall data ($r > .70$) and the small sample size restricting the number of comparisons to be performed.

The raw scores from the CVLT-II total learning trial, immediate and delayed recall trials and the recognition trials were converted to standard scores using published normative data that corrects for both age and sex. Validity studies of the Norwegian version of the CVLT-II have shown good fit between the Norwegian translation and American norms [28].

Visual-spatial abilities and crystallized intelligence were assessed by two subtests (Matrix Reasoning and Vocabulary) from the Norwegian version of the Wechsler Abbreviated Scale of Intelligence (WASI) [29]. The Vocabulary subtest demands that the examinee gives overt explanations of words with an increasing level of difficulty. The Norwegian version of the WASI has shown acceptable fit to American normative data [30]. The Matrix reasoning is a non-verbal subtest measuring visual-perceptual- and problem solving ability. WASI scores are converted to standardized scores by normative data, correcting for age, but not sex.

2.3. MRI acquisition

Subjects were scanned in a 1.5 Tesla Phillips Intera MR scanner using an 8-channel head coil. The T1-weighted structural scans were 3D turbo field echo scan with TR = 1.825 ms, TI = 855 ms, TE = 4.0 ms, flip angle = 8°, and voxel resolution = 0.94 x 0.94 x 1.25 mm^3. The MRI scanning was performed within a month after cognitive testing for all participants.

2.4. Volumetric MRI analysis

Hippocampal subfields were calculated by an automated segmentation process [31] implemented in Freesurfer 6.0 (https://surfer.nmr.mgh.harvard.edu/). FreeSurfer automatically labels each voxel of the T1 MR-images to one of 40 predefined structures by using probabilistic brain atlases [32-34]. In the present study, the volumetric data for the hippocampal subfields, estimated total intracranial volume and total left and right hippocampus volumes were used. See Figure 1 for an example of segmentation based on Freesurfer 6.0 from the present study. The volumes used in the correlation analyses were adjusted for age, sex and estimated total intracranial volume (eTIV). The adjustments were performed by linear regressions where brain volumes were dependent variables, and age, sex and eTIV were entered as predictors. The standardized residuals from the regressions were then saved and used for the analyses. The adjusted volumes (residuals) for the left and the right Cornu Ammonis (CA) CA1, CA2/3, CA4/Dentate Gyrus (DG), presubiculum, subiculum and the total volumes of the right and the left hippocampus were correlated with performance on cognitive tests.

2.5. Statistical analyses

The distribution of the calculated residuals was not significantly different from a normal distribution shown by the Shapiro-Wilk test, and this was further confirmed by inspection of Q-Q plots of the residuals. Thus, parametric statistical testing was performed. Independent samples t-test were used to test group-differences in unadjusted volumes. Paired samples t-tests were used to compare differences between the left and the right hippocampal formations. Correlations between hippocampal volumes and CVLT II subtests were performed with Pearson correlations, and in order to adjust p-values for multiple testing and reducing the probability of type I errors, p-values were adjusted with the False Discovery Rate (FDR) procedure with q = .05 [35, 36]. After FDR adjustments performed with a script for SPSS

(http://www-01.ibm.com/support/docview.wss?uid=swg21476447) the level of significance was $p < .0044$ for the correlational analyses between cognitive performance and hippocampal subfields. Elsewhere, p-values $< .05$ were considered significant. To test whether correlations were significantly different based on their z-score distribution, the Fisher r-to-z transformation test was employed.

3. Results

3.1. Cognitive data

Descriptive data for CVLT II, WASI, and volumetric measures are presented in Table 1. The sample means of the cognitive tests were within one standard deviation from the normative means, however, the results on the CVLT II showed that one abnormally low score (below 2 SD from the normative mean) from separate participants occurred on all CVLT subtests. All participants performed within the statistical normal range (T-score > 40) measured by the WASI tests, and the frequency of abnormal scores was not deviant from other studies using neuropsychological methodology [37]. There were no significant sex differences in CVLT II adjusted scores (all t's < 1.82), but females performed better compared to males based on the unadjusted raw scores on the recognition subtest ($t(45) = 2.26$, $p = .03$). No other comparison between males and females performance on the CVLT II reached significance.

3.2. Unadjusted volumetric data

Males had larger right hippocampus ($t(45) = 2.15$, $p = .037$) and larger eTIV ($t(45) = 5.07$, $p < .001$), but there was no sex difference in left hippocampal volume ($t(45) = 1.17$, $p = .25$). There were significant differences in volumes between the left and the right hemisphere on the hippocampal subfield measures shown by paired samples t-tests (all t's $(46) < 5.01$, all p's

< .001) with exception of the comparison left versus right subiculum (t (46) = .45, p = .65). The right subfields were larger (p < .05) compared to the left subfields, with the exception of the left presubiculum being larger than the right (t (46) = 5.03, p < .001). All t-tests on the left versus right comparisons of volumetric data are presented in Table 2. Univariate Pearson correlations between the left hippocampus, the right hippocampus and total hippocampal size and age and eTIV revealed that age had no significant association with any of the volumetric data, but there was a non-significant tendency to negative correlations between age and volumes. eTIV was significantly associated with left hippocampal volume (r = .49, p < .01), right hippocampal volume (r = .59, p < .001) and total hippocampal volume (r = .55, p < .001).

3.3. Correlation analyses on data adjusted for age, sex and eTIV.

The correlation analyses showed that there were no significant associations between the right hippocampal subfields residuals and the CVLT II subtests. There were several significant correlations (p < .05) between the CVLT II subtests and left hippocampal subfields residuals, however when applying the FDR adjustments (p <.0044), only the CA1, CA2/3 and the CA4 had significant associations with verbal memory performance (Table 3 and Figure 2). There were no significant correlations between performance on the WASI and hippocampal measures when adjusting p-values with the FDR procedure. The Fisher r-to-z transformation tests showed that none of the significant correlations between subfields in the left and CVLT II performance was significantly different from the same correlations in the right subfields when using the z-score as criterion. The z-scores of the difference ranged from z = 1.34, p = .09 to z = .99, p = .16 (one-tailed). The correlations between the merged (left + right) subfields and CVLT II performance showed that larger volume of the CA1 was significantly associated with better delayed recall performance. However, the whole hippocampus, the CA2/3 and the CA4/DG had correlations with all CVLT II measures with the exception of the

recognition score, but the significance of these correlations did not pass the FDR criterion (see Table 3).

4. Discussion

In accordance with our hypothesis, the present results showed significant associations between larger volumes of the left hippocampal subfields (CA1, CA2/3, CA4/DG) corrected for age, sex and eTIV with verbal learning and memory performance. Specifically, volume of the CA1 correlated with delayed recall, whereas volume of the CA2/3 was related to immediate and delayed recall, and volume of the CA4/DG were significantly associated with learning, immediate and delayed recall. Volumes of the right hippocampal subfields were not significantly related to verbal learning or recall performance. This lateralization effect in hippocampal subfields is not previously shown for verbal memory tests that include list learning, which is the type of test most commonly used for measuring verbal episodic memory [27]. Two previous studies [20, 21] found a similar effect of the whole left hippocampus without separating the subfileds. Moreover, a recent study by Palombo et al., [15] found that performance on the Autobiographical Interview [38] correlated significantly with the left CA2/3 but not the right CA2/3.

The analyses of structural volumes showed that the right CA1, CA2/3 and the CA4/DG were larger compared the same structures in the left hemisphere. The presubiculum was the only subfield in the left hippocampus being larger than the subfields in the right hemisphere. This is in line with several previous studies [22-24] on healthy volunteers showing a structural asymmetry of hippocampal volumes. In patients with Alzheimer's disease, episodic memory deficits are more associated with volumes of the left subfields compared to the right subfields [39], and the structural asymmetry of the hippocampal volumes is absent. It has been

suggested that the left compared to the right hippocampus is more affected by atrophy caused by vascular and neurodegenerative processes in Alzheimer's disease [40]. Thus, the episodic verbal memory deficits in Alzheimer's disease could to some extent be caused by increased left hippocampus vulnerability compared to the right hippocampus [41]. Taken together, several studies in both healthy volunteers and patients suggest that the left hippocampus is more involved in verbal episodic memory in healthy volunteers compared to the right hippocampus.

Previous studies have suggested that CA2/3 and CA4/DG are structures more related to encoding and learning than recall, whereas the CA1 is an output structure mainly related to retrieval functions [42-44]. The results from the present study support these suggestions, except that volumes of the CA2/3 and the CA4/DG were related to performance in the recall stage of verbal memory, and not solely associated with the learning phase. This is in line with a 7 Tesla fMRI study showing that the CA2/3 and CA4/DG are activated both during learning and recall, however more in the learning phase [45]. In comparison to Zammit et al [12], we did not find any correlation between volume of the left or right subiculum and verbal memory. Zammit et al [12] used only data for the merged left and the right subfields in their analyses in contrast to the present study.

The partially divergent findings on the relation between hippocampal morphometric data and verbal memory performance may be due to several methodological differences between studies. Different verbal memory tests have been employed across volumetric studies on hippocampal subfields. The Free and Cued Selective Reminding Test [12], The Autobiographical Interview [15] and the Wechsler Memory Scale (WMS-IV) [8] have been used in healthy samples, whereas the WMS-III [46], the CVLT [17, 46] and the Brief Assessment of Cognition in Schizophrenia [47] have been used in studies with mixed samples of healthy controls and patients. Even if tests for episodic verbal memory are highly

correlated, the concordance is not perfect between tests [48, 49]. Hence, different tests designed for measuring episodic memory might measure different aspects of the construct and may produce variability in hippocampal correlates. In addition, Zammit et al [12] employed FreeSurfer for automatic volumetric segmentation in healthy volunteers, whereas Travis et al [8] and Palombo et al [15] used a manual segmentation procedure. Different methods for estimating volume may produce small but measurable differences in estimates of cerebral structures [50]. Additionally, the age span in studies on healthy volunteers differ across studies, from participants below 35 years [8, 15] to elderly with a mean age at approx. 79 years [12]. The present study recruited volunteers in the age span 20 to 71 years, but there were no significant linear association between unadjusted hippocampal volumes and age. Previous studies have suggested that the linear effect of age is small, but still significant with negative correlations between age and volume in healthy cognitively preserved elderly [51], even if the rate of age-releated athrophy is suggested to be low ($\leq 0.2\%$ per year) [52]. On the other hand, age effects and brain maturation do often show complex and non-linear patterns and other statistical models than the linear approach might be better suited for this purpose [53]. Furthermore, even if there were no significant association between age and unadjusted hippocampal subfield volumes in the present study, previous studies have found that structural changes of the hippocampus during development may contribute to age-related differences in episodic memory [54]. In healthy elderly, a positive relationship between preserved memory functions and hippocampus volume is generally supported, even if some studies found no such association or a negative association, for an overview see Kaup et al. [9].

Females perform generally better on tests related to episodic memory compared to males, and the CVLT II norms are adjusted for sex [16]. Data from the present study did not show any sex difference on adjusted CVLT II scores, but females performed better on the recognition subtest based on the unadjusted raw scores. The lack of sex differences in the CVLT II raw

score data may be attributed to the small sample size and the educational level of the participants. Furthermore, there are sex differences in hippocampal subfield volumes where females have larger volumes than males adjusted for intracranial volume, but males and females display similar decrease of hippocampal volumes with age [52]. In the present study, we adjusted for both the effects of sex and age in the correlation analyses between CVLT performance and volumetric data, and the results cannot inform about the impact of sex and age on episodic memory.

The main limitations of the present study are the small sample size and the large variability in age of the included participants. The Fisher r-to-z transformation tests showed that the distributions based on the correlations in the left and the right subfields did not differ significantly, even if the FDR-adjusted p-value from the correlations were significant. Furthermore, when using the FDR correction for controlling familywise error rates, there is a risk of type-II errors when rejecting correlations with p-values close to the FDR criterion. Hence, the generalizability of the findings is questionable and the results should be regarded as preliminary findings that need conformation in larger samples. Nonetheless, the significant results were in line with findings from studies with related methodology [8, 15, 17, 18]. Several associations between hippocampal subfields volumes and verbal memory were close to significance, and a larger sample may have provided clearer findings. The Freesurfer segmentation process implemented in earlier versions (5.3 and earlier) of the software has received criticism for providing inaccurate estimates that conflicts with structural findings in anatomical studies [55]. In this study, we used Freesurfer 6.0 where the accuracy and correspondence with anatomical studies has been improved [31], and this version of Freesurfer has shown good test-retest reproductibility estimates for hippocampal segmentation in studies with large samples [56]. However, results based on 1mm segmentation of internal subfields such as the CA4 should be interpreted with caution and further validation of the

software with higher resolution should be performed to confirm the results. Thus, improvements in software and increased field-strength of MR-images might produce more accurate findings in future larger studies.

5. Conclusion

In summary, the present study showed that verbal learning, immediate- and delayed recall measured by the CVLT II had significant relations with separate subfields of the left hippocampus in healthy adults in the ages between 22 to 71 years. Furthermore, there were no significant associations between the right hippocampal subfields and verbal memory performance suggesting that auditory verbal memory is associated with volumetric lateralization effects in the hippocampus. The present results should be replicated in larger samples, and should be interpreted with caution due to the small sample size and large variability in age of the included participants.

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