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Novel characterization of the relationship between verbal list-learning outcomes and hippocampal subfields in healthy adults

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Abstract

The relationship between hippocampal subfield volumetry and verbal list-learning test outcomes have mostly been studied in clinical and elderly populations, and remain controversial. For the first time, we characterized a relationship between verbal list-learning test outcomes and hippocampal subfield volumetry on two large separate datasets of 447 and 1,442 healthy young and middle-aged adults, and explored the processes that could explain this relationship. We observed a replicable positive linear correlation between verbal list-learning test free recall scores and CA1 volume, specific to verbal list learning as demonstrated by the hippocampal subfield volumetry independence from verbal intelligence. Learning meaningless items was also positively correlated with CA1 volume, pointing to the role of the test design rather than word meaning. Accordingly, we found that association-based mnemonics mediated the relationship between verbal list-learning test outcomes and CA1 volume. This mediation suggests that integrating items into associative representations during verbal list-learning tests explains CA1 volume variations: this new explanation is consistent with the associative functions of the human CA1.

KEYWORDS
association-based mnemonics, healthy young adults, hippocampal subfields, reliability, structural MRI, verbal list-learning

1 | INTRODUCTION

The hippocampal formation (referred to as the *hippocampus* hereafter) is a bilateral structure nested in the medial temporal lobe of the human brain. The hippocampus is composed of structural and functionally distinct subfields in which deterioration leads to severe memory disorders (Small, Schobel, Buxton, Witter, & Barnes, 2011). Notably, Alzheimer's disease (AD) is associated with a wide range of hippocampal structural changes, including subfield atrophy (Maruszak & Thuret, 2014). Indeed, subfield volumetry has become a more promising method to detect incipient AD than total hippocampal volumetry. Selective atrophy of hippocampal subfields, especially of the cornu ammonis (CA) 1, subiculum, and presubiculum, predicts AD's early-onset (Abraham et al., 2020; Broadhouse et al., 2019; Carlesimo

et al., 2015; Hanseeuw et al., 2011; Hata et al., 2019; Jacobs et al., 2020; La Joie et al., 2013; Lindberg et al., 2017; Ogawa et al., 2019; Parker et al., 2018; Vasta et al., 2016) and conversion from mild cognitive impairment or diagnoses (Apostolova et al., 2010; Chételat et al., 2008; Hata et al., 2019; Khan et al., 2015; Nadal et al., 2020; West, Kawas, Martin, & Troncoso, 2006).

Supraspan verbal list-learning tests (VLTs) are standard neuropsychological measures for assessing verbal declarative memory in aging and clinical studies. VLTs are also efficient in identifying or predicting conversion to AD (Bauer, Cabral, & Killiany, 2018; Cerami et al., 2017; Estévez-González, Kulisevsky, Boltes, Otermín, & García-Sánchez, 2003; Fleisher et al., 2008; Gleason et al., 2017; Goryawala et al., 2015; Moradi, Hallikainen, Hänninen, & Tohka, 2017; Vuoksimaa et al., 2018), to the extent of being considered markers of hippocampal integrity (Saury & Emanuelson, 2017).

Hence, according to the literature, VLT outcomes and hippocampal subfield volumetry (HsVol) are two predictors of AD that have controversial relationships. Twenty-three studies in the last 10 years have investigated the relationship between VLT-free recall scores and the volume of CA1, CA3, CA4, dentate gyrus (DG), presubiculum, or subiculum (the full review is provided in the Supporting Information). The majority of the studies reviewed did not find any link between VLT-free recall scores and HsVol, demonstrating the challenge of highlighting such a relationship. However, a positive and linear VLT–HsVol relationship has been reported in 33–47% of the studies (according to the subfield) and localized either in the left cerebral hemisphere or in both hemispheres. Almost all studies with positive findings used 3T (or higher) magnetic resonance imaging (MRI) acquisition. They also typically used the most recent hippocampal automated parcellation techniques (FreeSurfer 6.0) in large datasets (greater than 200 participants). In contrast, variations in statistical modeling or the type of VLT-free recall score (immediate vs. delayed) do not seem to impact whether a given study reported significant VLT–HsVol relationships.

Studies that detected a significant VLT–HsVol relationship share some similarities across hippocampal subfields. Both the CA1 and CA3 volumes show significant relationships with VLT outcomes regardless of the health status or age range of the sample (Aslaksen, Bystad, Ørbo, & Vangberg, 2018; Broadhouse et al., 2019; Carey, Nolan, Kenny, & Meaney, 2019; Gicas et al., 2019; Mueller, Chao, Berman, & Weiner, 2011; Xiu et al., 2020; Zammit et al., 2017; Zheng et al., 2018). In contrast, the relationships between VLT outcomes and the CA4, DG, and presubiculum are most frequently observed in clinical and elderly samples (Aslaksen et al., 2018; Broadhouse et al., 2019; Carey et al., 2019; Carlesimo et al., 2015; Jacobs et al., 2020; Lim et al., 2013; Lim et al., 2012; Mueller et al., 2011; Stav et al., 2016; Uribe et al., 2018; Zheng et al., 2018). Finally, the relationship between VLT outcomes and the subiculum is almost exclusively observed in elderly populations, regardless of the individual's health status (Carlesimo et al., 2015; Hartopp et al., 2019; Lim et al., 2013; Lim et al., 2012; Stav et al., 2016; Uribe et al., 2018; Zammit et al., 2017; Zhao et al., 2019; Zheng et al., 2018).

We noticed a crucial point missing in the reported examination of the relationship between VLTs and HsVol; *prior* research has omitted to explore *why* VLT-free recall performance is related to specific hippocampal subfields. Explaining the VLT–HsVol relationship is crucial for a better understanding of the hippocampal processes involved (Salmon, 1978), which will help refine the neurodegenerative markers in the design of neuropsychological testing on the one hand and neuroanatomical targeting on the other.

Among the 23 studies we reviewed, only eight involved young adults under 35 years of age, with a high average age ranging from 28 to 55 years. Hence, we began by describing the HsVol in relation to VLT outcomes in a large dataset of healthy young and middle-aged adults before they experience significant aging or disease-related impacts. In particular, we wished to target a healthy population under 60 years of age, a tipping point toward visible atrophy of the hippocampus and its subfields (Bussy et al., 2021; Carey et al., 2019; Fjell, 2013). To our knowledge, this population has never been explicitly targeted in this regard. Therefore, we investigated whether the individual difference in the VLT-free recall performance explained HsVol compared to the whole hippocampal volume. Given our literature review, we expected a gain in sensitivity with subfield-level volumetry, namely, positive correlations between VLT-free recall performance and bilateral CA1 and CA3 hippocampal volumes. To test the specificity of the VLT–HsVol relationship, we also tested the relationship between verbal intelligence and HsVol. Importantly, to establish the reliability of our findings (National Academies of Sciences, Engineering, and Medicine, 2019), we replicated the whole analysis with a second large independent dataset of healthy young adults.

We further explored two neuropsychological processes that could explain the VLT–HsVol relationship. First, the items of VLTs are concrete words in which the meaning partially determines recall performance (Cremona, Jobard, Zago, & Mellet, 2020). To test the role of a *meaning-based* hippocampal computation, we replicated the paradigm with *pseudowords* similar to words except that they are meaningless. If meaning-based hippocampal processing explains the VLT–HsVol relationship, we expect a distinct VLT–HsVol relationship when items in the learning list are words compared to pseudowords. Second, the supraspan length of VLT lists encourages mnemonics based on intra- and extralist associations (Cremona et al., 2020; Gross & Rebok, 2011; Worthen & Hunt, 2017), and the hippocampus is thought to contribute to the formation of representations composed of associations among multiple elements (Dalton, Zeidman, McCormick, & Maguire, 2018; Jabès & Nelson, 2015; Moses & Ryan, 2006). If an *association-based* hippocampal computation explains the VLT–HsVol relationship, we expect self-reported association-based mnemonics to mediate this relationship.

2 | METHODS

2.1 | Participants

Sample 1. To explain the VLT–HsVol relationship, we used data collected from a dataset including a battery of 10 cognitive tests and enriched with left-handers in order to study brain hemispheric

specialization (BIL & GIN; Mazoyer et al., 2016). Participants were native French speakers, were free from developmental disorders, had no neurological and psychiatric history, and were aged 18–57 years (mean age = 26.6). Sample 1 was biased toward young adults, and participants under 35 years (max-age of Sample 2) accounted for 88% of the sample. The Basse-Normandie Ethics Committee approved the study protocol that was conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave their informed written consent and received compensation for their participation. Four participants missing VLT data and two participants suspected of having dyslexia were excluded from the present study ($n = 447$). All participants in Sample 1 completed the VLT, pseudoword version of the VLT (pseudoword-LT), and vocabulary test (see Section 2.2).

Sample 2. To test the reliability of the findings of Sample 1, we used data collected from the Internet-based Students Health Research Enterprise (i-Share) project, a large prospective cohort of French university students aged 18–35 years investigating student health status (https://research.i-share.fr/). The i-Share project was approved by the French National Commission of Informatics and Liberties and conducted in accordance with the guidelines of the Declaration of Helsinki. Students registered voluntarily, completed a mandatory baseline questionnaire and an optional questionnaire aiming to investigate cognitive functioning through a shorter computer version of the BIL & GIN's cognitive battery. Volunteers could also participate in the neuroimaging component of the i-Share project dedicated to studying neuroanatomical maturation in healthy young adults (MRi-Share; Tsuchida et al., 2020). The Bordeaux CPP SOMIII Ethics Committee approved the MRI protocol. All participants gave their informed written consent and received compensation for their participation. Among the 1870 MRi-Share participants, native French speakers with usable MRI data were selected and combined with those who underwent the VLT (*Sample 2.1*, $n = 1{,}242$, mean age = 22) or vocabulary test (*Sample 2.2*, $n = 1{,}341$, mean age = 22). We used the maximum sample size for each variable to maximize the statistical power of the subsequent analyses. Sample 2.1 and Sample 2.2 shared 979 participants and had similar demographics and volumetry (Table 1a,c). None of the participants from Sample 2 performed pseudoword-LT.

2.2 | Cognitive assessments

In aging and clinical studies, VLTs are commonly included in cognitive batteries to assess verbal declarative memory given their ease of use and the wide variety of scores they provide (Lezak, Howieson, Bigler, & Tranel, 2012). All VLTs consist of learning a supraspan list of concrete words, that are either related or not. VLTs are divided into an encoding and a retrieval phase.

In the present study, a list of unrelated nouns (18 in Sample 1, 15 in Sample 2) was presented to the participants at a rate of one word per second. The list was read aloud by an experimenter in Sample 1 and displayed on a computer screen in Sample 2. At the end of the presentation, the participants were instructed to freely recall as many words as possible. The recall was oral in Sample 1 and typed on a keyboard by participants in Sample 2, ending the trial. The number of encoding trials was 5 in Sample 1 and 1 in Sample 2. Twenty minutes after the last encoding trial (Trial 5 in Sample 1, Trial 1 in Sample 2), each participant was asked to recall the list again without resubmitting it. Thus, the 20 min-delayed recall corresponded to Trial 6 in Sample 1 and Trial 2 in Sample 2. The raw score of each trial was the number of words correctly recalled. According to the available data in Sample 2 and to replicate the same analysis in both samples, we created a compound VLT-free recall score by adding Trial 1 to Trial 2. Of note, Trials 2 in both samples shared a similar normal distribution and a high level of correlation with Trial 1 (Spearman's *rho*: Sample 1 = 0.65, Sample 2 = 0.77), despite the presence of the 20-min

TABLE 1 Descriptive data —*n* (%)/mean (*SD*, range)

	Sample 1 ($n = 447$)	Sample 2.1 ($n = 1{,}242$)[a]	Sample 2.2 ($n = 1{,}341$)[a]
a. Demographics			
Sex (female)	228 (51%)	911 (73.3%)	1,007 (75.1%)
Handedness (right-handers)	244 (54.6%)	1,084 (87.3%)	1,174 (87.5%)
Age (years)	26.61 (7.6, 18–57)	21.98 (2.2, 18–32)	22.03 (2.3, 18–35)
Education (years)	15.27 (2.5, 8–20)	14.75 (1.7, 13–21)	14.70 (1.7, 13–21)
b. Cognitive scores			
VLT (max. S1: 36/S2: 30)	19.85 (3.8, 9–33)	15.81 (3.4, 6–28)	–
Pseudoword-LT (max. 75)	33.96 (11.8, 2–60)	–	–
Vocabulary (max. S1: 44/S2: 8)	27.47 (4.2, 15–36)	–	5.25 (1.5, 0–8)
c. Freesurfer global volumetry			
eTIV ($mm^3 \times 10^3$)	1,423.13 (141.7)	1,563.89 (138.4)	1,560.66 (135.3)
Whole hippocampus left (mm^3)	3,203.85 (318)	3,502.77 (337.9)	3,503.05 (338.9)
Whole hippocampus right (mm^3)	3,241.29 (318.6)	3,493.17 (336.4)	3,491.49 (338.5)

[a]Samples 2.1 and 2.2 shared 979 participants.

delay in Sample 2. As trials repetition acts on memory processes (Henke, 2010), this procedure ensures an equal number of trials between the two samples.

VLT outcomes positively correlate with verbal intelligence assessed by vocabulary testing (Bolla-Wilson & Bleecker, 1986). We replicated this result in both samples (Figure S1). To check whether the VLT–HsVol relationship is driven by verbal intelligence, we examined the relationship between HsVol and vocabulary extent assessed through the pinpointing of synonyms (adapted from [Binois & Pichot, 1956]). For each trial (44 in Sample 1, 8 in Sample 2), a target word was presented at the top of the screen, and six alternatives were displayed below with a prefix number. The participants had to press the button number that correctly matched the synonym for the target word within a delay of 30 s. Trials were classified in order of increasing difficulty. The raw score was the number of correct trials (Table 1b).

To explore whether the VLT–HsVol relationship relies on a meaning-based hippocampal computation, we compared it to the relationship between the HsVol and a pseudoword-LT in Sample 1. A procedure similar to that of word encoding was applied using 15 meaningless pseudowords. Pseudowords were created with the WordGen software (Duyck, Desmet, Verbeke, & Brysbaert, 2004) and matched to the list of words by the number of letters, phonemes, syllables, and bigram frequencies. This task was more difficult than the word task, leading to lower raw scores. We chose the frequently used *total learning* score (i.e., the sum of the five encoding trials; Lezak et al., 2012), as the raw score that best reflects the interindividual variability of the pseudoword-LT outcomes (Table 1b).

Finally, to explore whether an association-based hippocampal computation explains the VLT–HsVol relationship, we collected mnemonics reported by the participants to retain the list of words in Sample 1. The method is detailed in Cremona et al. (2020). In short, 377 participants reported association-based mnemonics, grouping words from either their meaning (semantic clustering) or position in the list (temporal clustering). Sixty-seven participants used a strategy based on listening, a minimal strategy directly arising from the auditory presentation of the list. Of note, the data of three participants were missing.

All on-screen testing was conducted with E-Prime (Version 2, Pittsburgh, PA: Psychology Software Tools.).

2.3 | MRI acquisition and processing

Sample 1. Brain structural anatomy was acquired using a 3T Philips Achieva MRI scanner (Philips Medical Systems, Best, NL). High-resolution T1-weighted (T1w) was obtained using a 3D-FFE-TFE sequence (TR = 20 ms, TE = 4.6 ms, inversion time = 800 ms, flip angle = 10°, matrix size = 256 × 256 × 180, and isotropic voxel size—1 mm^3).

Sample 2. Brain structural anatomy was acquired using a 3T Siemens Prisma MRI scanner (Siemens Healthineers, Erlangen, DE) with a high-resolution 3D MPRAGE T1w sequence (TR = 2000 ms, TE = 2.03 ms, inversion time = 880 ms, flip angle = 8°, slices = 192, in-plane acceleration = 2, matrix size = 192 × 256 × 256, and isotropic voxel size—1 mm^3) and 3D SPACE fluid attenuation inversion recovery (FLAIR) sequence (TR = 5,000 ms, TE = 394.0 ms, inversion time = 1800 ms, in-plane acceleration = 2, partial Fourier 7/8, matrix size = 192 × 256 × 256, and isotropic voxel size—1 mm^3).

For each participant, the line between the anterior and the posterior commissures was identified on a mid-sagittal section, and the volume was acquired after orienting the brain according to the bicommissural coordinate system. A trained radiologist assessed the structural T1w scans of all subjects, and all subjects were found to be free of brain abnormalities.

2.4 | Hippocampal subfield segmentation

In both samples, hippocampal subfield volumes were obtained with the HippoSubfield module in FreeSurfer 6.0 (https://surfer.nmr.mgh.harvard.edu/fswiki/HippocampalSubfields), a segmentation tool based on a probabilistic atlas built from ultrahigh-resolution ex vivo MRI data (~0.1 mm isotropic; Iglesias et al., 2015). For Sample 1, hippocampal subfield volumes were obtained by processing the T1w images. T1w scans of 1 mm^3 are commonly used in large cohort studies, such as the UK-Biobank (Alfaro-Almagro et al., 2018; for examples of hippocampal subfield volumetry studies: Foo et al., 2021; Majrashi, Ahearn, Williams, & Waiter, 2020) or the Dallas LifeSpan Brain Study (https://dlbsdata.utdallas.edu/StructuralMriProtocol; Zheng et al., 2018), where they represent optimized imaging sequence both in terms of spatial resolution and acquisition time, given the large size of the samples studied. A recent commentary has cautioned against using HsVol obtained from 1 mm isotropic T1w scans (Wisse et al., 2021). However, the authors of the Freesurfer hippocampal subfield segmentation algorithm have demonstrated the empirical utility of the subfield segmentation based on 1 mm isotropic T1w images by showing the improved accuracy in discriminating between subjects with and without AD (Iglesias et al., 2015). As detailed in a recent review (Sämann et al., 2020), the Freesurfer hippocampal subfield segmentation with 1 mm isotropic T1w scans has been applied in a wide range of domains, including cognition in healthy and clinical populations, and show good measurement reliability and clinical validity. Others, studying young and middle-aged adults, have shown good consistency (a Pearson's correlation > = .9) between subfield segmentation based on 1 mm isotropic T1w and the recommended high in-plane resolution (0.4 mm) T2-weighted (T2w) images in all subfields we examined here, except for CA3 (Broadhouse et al., 2019). Although the method should be robust with the standard 1 mm isotropic T1w images, having T2w scans as the additional input improves the segmentation accuracy by providing contrasts for important landmark structures, especially if they are of higher resolution than the main T1w image (Iglesias et al., 2015). For this reason, for Sample 2 in which 1 mm isotropic FLAIR scans were available, we used both T1w and FLAIR images as the inputs to the HippoSubfield module to obtain the subfield volumes.

The HippoSubfield module produced an automated parcellation of the left and right hippocampal formations in 12 subfields for each participant. The hemispheric whole hippocampal volumes were

obtained by adding the 12-subfield volumes. The present study focused on subfields that have been repeatedly related to VLTs, that is, the CA1, CA3, CA4, DG, presubiculum, and subiculum subfields (Figure 1 and Table S1).

The estimated total intracranial volume (eTIV) was extracted as a direct output of the FreeSurfer 6.0 routine (Table 1c).

Hippocampal subfield volumes are highly correlated within and between the hemispheres. In addition, volumes are substantially different from one sample to another, and in a given sample, some subfields are larger than the others (Figure 1 and Table S1). As a result, the use of the raw values may lead to distortions in the estimation of their variations. For these reasons, each subfield volume was normalized to the whole hippocampal volume (Evans et al., 2018; Izzo, Andreassen, Westlye, & van der Meer, 2020; Sämann et al., 2020; Uribe et al., 2018), and the random effects were fitted with mixed-effect models (Carey et al., 2019). The effect of the hemispheric whole hippocampal volume on each hippocampal subfield volume was first regressed out. Residuals of these linear regressions were standardized to be used as the dependent variables in subsequent mixed-effect models.

2.5 | Statistical analyses

All statistical analyses were conducted with R Version 4.0.0 (R Core Team, 2020). All the numeric variables (i.e., age, education, and eTIV) were standardized in z-scores, and categorical variables (i.e., sex, hemisphere, and subfield) were coded as factors. The alpha level of 0.05 or the 95% confidence interval (CI) was used for the significance threshold of hypothesis tests. Two-tailed tests were used for all analyses. For mixed-effect models, all post hoc analyses were Bonferroni-corrected for the multiplicity of tests (Lenth, 2020) and the unstandardized slope coefficient (*b*) with its CI was reported as effect size (Baguley, 2009).

2.5.1 | VLT–HsVol relationship

We first analyzed the relationship between the VLT score and the six hemispheric hippocampal subfield volumes in Sample 1. To this end, we ran a mixed-effect linear regression model with a three-way interaction term between VLT score × hemisphere × subfield (and all lower-order terms) as the fixed effect predictors and with volume as the dependent variable. To test the specificity of the VLT–HsVol relationship, we also examined whether verbal intelligence (i.e., vocabulary score) showed the same profile as that of VLT. Thus, we ran a mixed-effect linear regression model with a three-way interaction term between vocabulary score × hemisphere × subfield (and all lower-order terms) as the fixed effect predictors and volume as the dependent variable. We also checked whether the subfield-level volumetry provided additional information by testing the relation between the VLT score and the hemispheric whole hippocampal volumes. We ran a mixed-effect linear regression model with a two-way interaction term between VLT score × hemisphere (and all lower-order terms) as the fixed effect predictors and volume as the dependent variable.

All models included eTIV (Harding, 1998), age (Harding, 1998), quadratic age (Carey et al., 2019; de Flores et al., 2015; Li et al., 2014), education (Tang, Varma, Miller, & Carlson, 2017), and sex (Crivello, Tzourio-

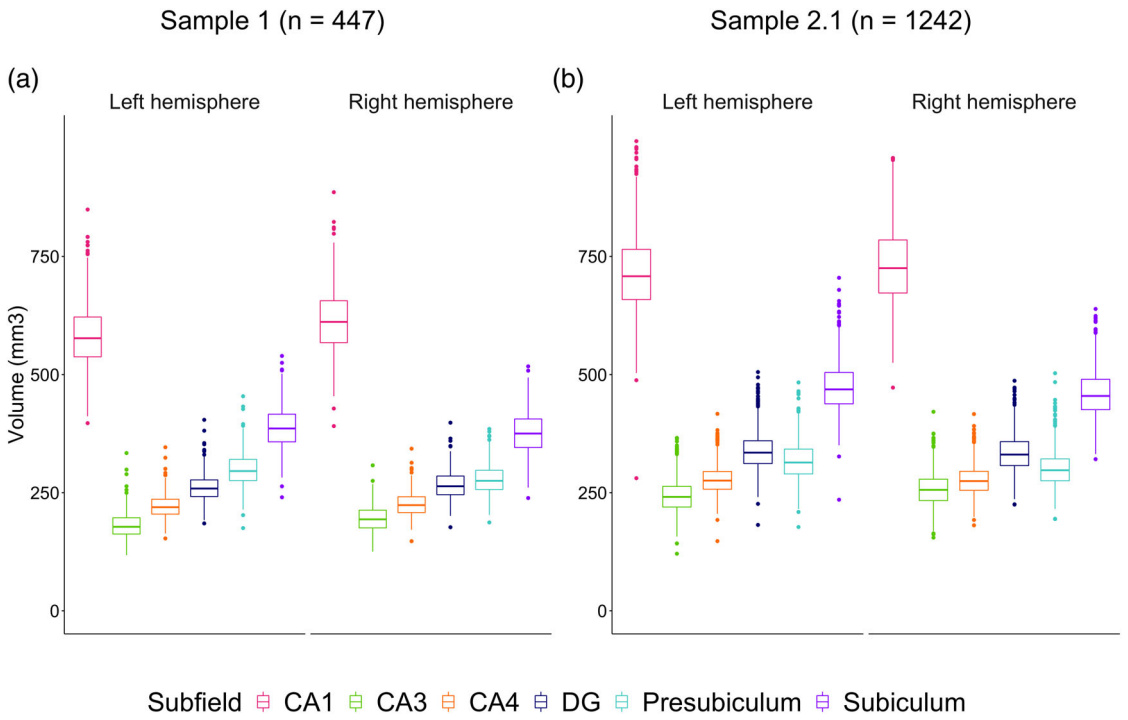

FIGURE 1 HsVol provided by Freesurfer 6.0. Mean volume (mm^3) of the six hippocampal subfields in left and right hemispheres of (a) Sample 1 and (b) Sample 2.1

Mazoyer, Tzourio, & Mazoyer, 2014) as fixed effect covariates. Random effects were fitted at the participant level, and the significance of fixed effects was assessed through ANOVA components estimated with the Kenward–Roger approximation to correct for underestimating variance (Bates, 2010; Halekoh & Højsgaard, 2014; Kuznetsova, Brockhoff, & Christensen, 2017). We used the likelihood ratio test for each model to estimate if the nonlinear age transformation improved the model fit, and we removed it from the model when it did not. The residuals were visually inspected for normality and homoscedasticity. Finally, a resampling bootstrap method was used with 1,000-fold replication to evaluate the uncertainty about fixed effect coefficient estimates and validate the internal reliability of the effects (Canty & Ripley, 2020). For all models, this method showed good consistency among fixed effect coefficient estimates.

2.5.2 | Replication of the VLT–HsVol relationship

To test the reliability of our findings, strictly identical statistical analyses to those applied in Sample 1 were carried out in Sample 2.1 for VLT score and Sample 2.2 for verbal intelligence.

2.5.3 | Does meaning-based computation explain the VLT relationship with HsVol?

To evaluate the role of meaning-based hippocampal computation in the VLT–HsVol relationship, we replicated the analysis on the pseudoword-LT score in Sample 1.

2.5.4 | Do association-based mnemonics mediate the VLT relationship with HsVol?

Finally, we sought to test whether self-reported association-based mnemonics contribute to the VLT–HsVol relationship in Sample 1. Using the R *lavaan* package (Rosseel, 2012), we ran six separate causal mediation analyses with the VLT score as the predictor, association-based mnemonics as a mediator variable (dummy coded), and each hippocampal subfield volume as the dependent variable. We corrected all models for age and eTIV and set up 10,000 bootstrap samples to estimate the standard errors of the direct and indirect effects of the VLT score ($n = 444$, since three mnemonic data points were missing).

3 | RESULTS

3.1 | The VLT score positively predicts the bilateral CA1, but not CA3, volumes

In Sample 1, we first tested our a priori hypothesis that the VLT score was a positive predictor of bilateral hippocampal CA1 and CA3 volumes. As expected, the VLT–HsVol relationship was different according to the subfield (Figure 2b; VLT score × subfield: $F[4895] = 3.39$, $p = .005$, $n = 447$) but not hemisphere (VLT score × hemisphere: $F(4895) = 0.14$, $p = .705$, VLT score × hemisphere x subfield: $F(4895) = 0.18$, $p = .971$, $n = 447$). The VLT score was positively related to CA1 volume (Figure 2a; $\beta = 0.10$, $SE = 0.35$, $t[3695] = 2.75$, $p = .006$, *p-Bon.* $= .036$, $b = 0.6$ [0.2–1.1]) but not CA3 volume or any other subfield (Figure 2a, b; Table S2). Using the unstandardized slope coefficient, we determined that the ability to recall an additional word was related to a mean larger CA1 volume of 0.6 mm^3, which represents a mean difference of 14 mm^3 between the best and worst performers.

Of note, verbal intelligence assessed by vocabulary score did not significantly predict overall HsVol or any specific subfields differentially (Figure 2c; vocabulary score: $F(441) = 2.21$, $p = .138$, vocabulary score x subfield: $F(4895) = 1.66$, $p = .140$, vocabulary score × hemisphere × subfield: $F(4895) = 0.23$, $p = .951$, $n = 447$), demonstrating the specificity of the VLT–HsVol relationship. Finally, we also demonstrated the gain in sensitivity provided by subfield-level volumetry by testing the relationship between the VLT score and whole hippocampal volumes in the left or right hemispheres. The VLT score did not predict either left or right whole hippocampal volume (Figure 2d; VLT score: $F(440) = 3.43$, $p = .065$, VLT score x whole hemisphere: $F(445) = 0.02$, $p = .888$, $n = 447$).

3.2 | The VLT–HsVol relationship profile and specificity are replicable

To ensure the reliability of our findings, we implemented an identical procedure, with some minor modifications (see Section 2), on a second independent sample of healthy young adults. We found that the results obtained in Sample 1 were highly reproducible in Sample 2. The VLT–HsVol relationship significantly varied according to the subfield (Figure 3b; VLT score x subfield: $F[13640] = 3.10$, $p = .008$, $n = 1{,}242$). Only the CA1 volume was positively related to the VLT score with a similar effect size as in Sample 1, representing a mean difference of 13 mm^3 in the CA1 volume of the best performers compared to the worst VLT performers ($\beta = .06$, $SE = 0.2$, $t[12699] = 2.94$, $p = .003$, *p-Bon.* $= .020$, $b = 0.6$ [0.2–1.0]; Figure 3a; Table S3). As in Sample 1, the VLT–HsVol relationship was independent of the hemisphere (VLT score x hemisphere: $F(13640) = 2.41$, $p = .120$, VLT score x hemisphere x subfield: $F(13640) = 0.57$, $p = .724$, $n = 1{,}242$). Moreover, the VLT-CA1 volume relationship was specific to the VLT since, again, verbal intelligence failed to predict HsVol overall or differentially for specific subfields (Figure 3c; vocabulary score: $F(1335) = 2.99$, $p = .084$, vocabulary score x subfield: $F(14729) = 1.98$, $p = .078$, vocabulary score × subfield × hemisphere: $F(14729) = 1.15$, $p = .332$, $n = 1{,}341$). Finally, there was no relation between the VLT score and whole hippocampal volume in either hemisphere (Figure 3d; VLT score: $F(1235) = 0.15$, $p = .697$, VLT score × whole hemisphere: $F(1240) = 0.02$, $p = .892$, $n = 1{,}242$), confirming the lack of sensitivity when using the whole hippocampal volume as the dependent variable.

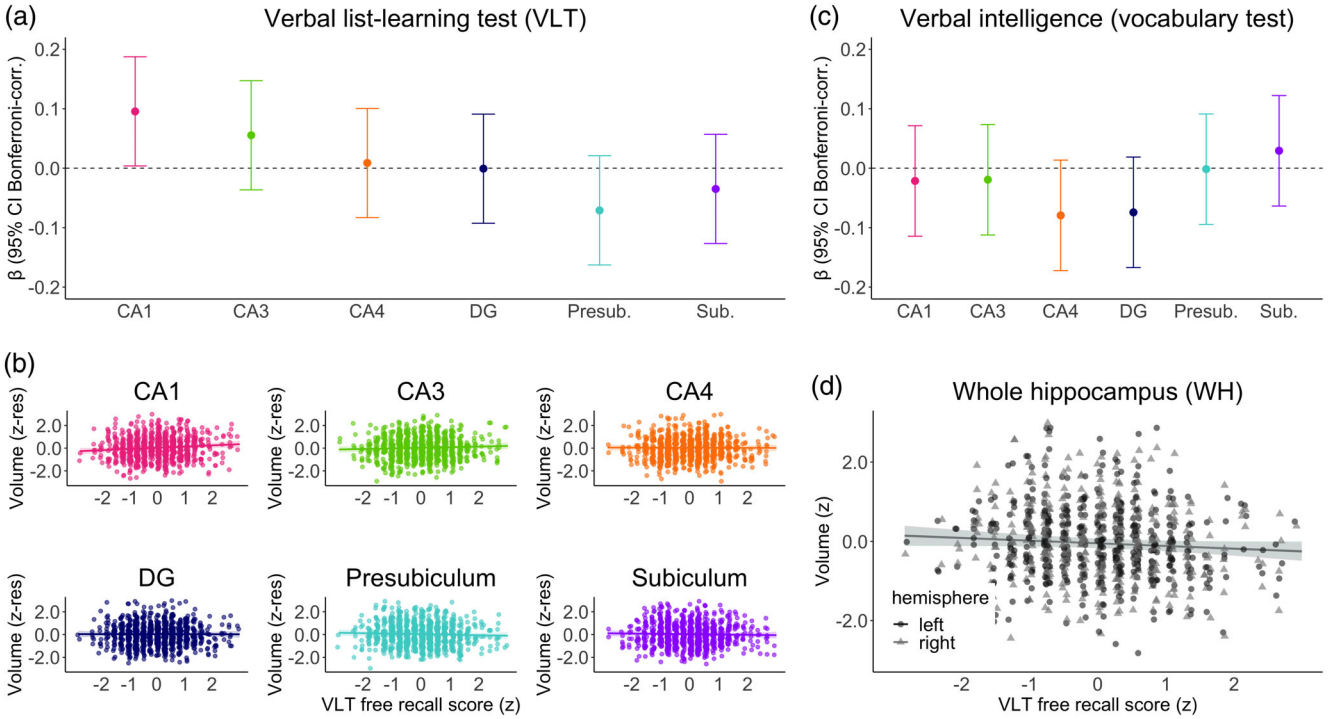

FIGURE 2 VLT–HsVol relationship profile and specificity in Sample 1. (a) Post hoc analyses of estimated subfield volume slopes related to the VLT score (+1 *SD*). Only the CA1 volume slope was related to the VLT score ($p = .036$, $n = 447$). (b) Scatter plots of CA1, CA3, CA4, DG, presubiculum, subiculum volumes, and the VLT score and each linear fitted line with its 95% CI. (c) Post hoc analyses of estimated subfield volume slopes related to verbal intelligence (+1 *SD*) assessed by vocabulary testing. No hippocampal subfield volume was related to verbal intelligence ($n = 447$). For (a, c), Bonferroni-corrected CIs and *p* values are reported. For (a–c), the residuals of hippocampal volumes were calculated by removing variance related to the hemispheric whole hippocampal volume. Models were adjusted for age, sex, education, and eTIV. (d) Scatter plots of left and right whole hippocampal volumes and VLT scores, and the linear fitted line with its 95% CI adjusted for age, age^2, sex, education, and eTIV. For (a–d), residual volumes, VLT scores, and vocabulary scores are transformed to *z*-scores. CI, confidence interval; eTIV, estimated total intracranial volume; HsVol, hippocampal subfield volumetry; VLT, verbal list-learning test

3.3 | The VLT-CA1 volume relationship is not explained by meaning-based computation

To determine whether the VLT-CA1 volume relationship could be explained by a meaning-based computation specific to words, we examined the relationship between the learning of meaningless items (i.e., pseudowords) and HsVol in Sample 1. The pseudoword-LT–HsVol relationship profile was highly similar to that of VLT outcomes, suggesting that the VLT–CA1 volume relationship was not dependent on verbal meaning processing. Indeed, we observed an interaction between the pseudoword-LT score and hippocampal subfields (Figure S2, pseudoword-LT score × subfield: $F(4895) = 2.79$, $p = .016$, $n = 447$). Again, only the CA1 volume was positively related to the pseudoword-LT score ($\beta = 0.12$, $SE = 0.36$, $t[3253] = 3.47$, $p = .001$, *p-Bon.* $= .003$, $b = 0.25$ [0.1–0.4]; Table S4), regardless of the hemisphere (pseudoword-LT score × hemisphere × subfield: $F(4895) = 0.70$, $p = .624$, $n = 447$).

3.4 | Association-based mnemonics mediate the VLT-CA1 volume relationship

Finally, to explore whether the use of association-based mnemonics could explain the VLT-CA1 volume relationship, we estimated the direct and indirect effects of the VLT score on HsVol in Sample 1 (Figure 4a). We observed that association-based mnemonics mediated the VLT-CA1 volume relationship (VLT indirect effect: ab = 0.017, $SE = 0.008$, $z = 2.04$, $p = .041$) but were not related to other hippocampal subfield volumes (Table S5). While the VLT score was significantly related to CA1 volume as expected (VLT total effect: c = 0.094, $SE = 0.046$, $z = 2.04$, $p = .042$), this link disappeared when taking association-based mnemonics into account (VLT direct effect: c' = 0.078, $SE = 0.047$, $z = 1.64$, $p = .101$; Figure 4b).

4 | DISCUSSION

We showed a positive linear relationship between VLT performance and CA1 volume in healthy young and middle-aged adults and found no link between VLT performance and the whole hippocampus. Verbal intelligence did not predict HsVol, confirming the specificity of the VLT–CA1 relationship. The VLT–CA1 volume relationship that we observed in two large independent cohorts reproduces previous results of studies in middle-aged adults and elderly populations (Aslaksen et al., 2018; Broadhouse et al., 2019; Carey et al., 2019; Gicas et al., 2019; Mueller et al., 2011; Zammit et al., 2017; Zheng et al., 2018); this is the first evidence that this relationship is

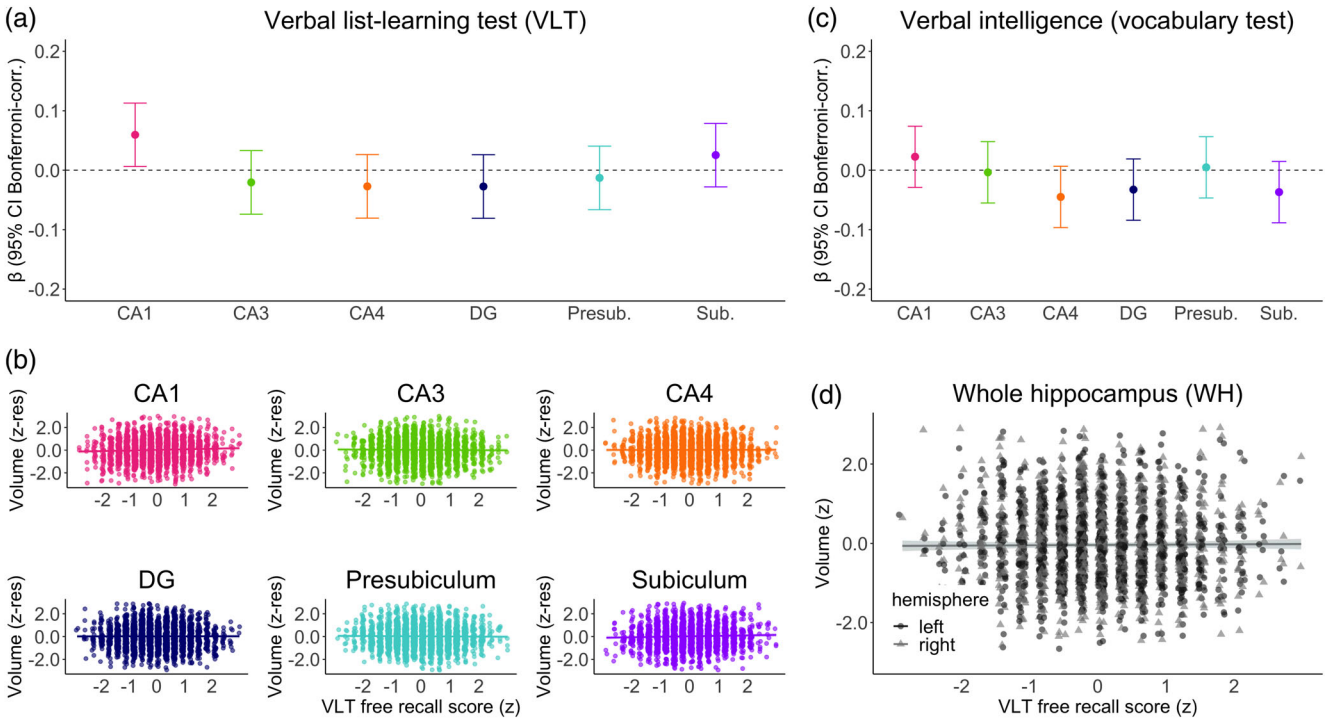

FIGURE 3 Replicability of the VLT–HsVol relationship profile and specificity in Sample 2. (a) Post hoc analyses of estimated subfield volume slopes related to the VLT score (+ 1 *SD*). Only the CA1 volume slope was related to the VLT score ($p = .020$, $n = 1{,}242$). (b) Scatter plots of CA1, CA3, CA4, DG, presubiculum, subiculum volumes, and the VLT score and each linear fitted line with its 95% CI. (c) Post hoc analyses of estimated subfield volume slopes related to verbal intelligence (+ 1 *SD*) assessed by vocabulary testing. No hippocampal subfield volume was related to verbal intelligence ($n = 1{,}341$). For (a, c), Bonferroni-corrected CIs and *p* values are reported. For (a–c), the residuals of hippocampal volumes were calculated by removing variance related to the hemispheric whole hippocampal volume. Models were adjusted for age, sex, education, and eTIV. (d) Scatter plots of left and right whole hippocampal volumes and VLT scores and the linear fitted line with its 95% CI adjusted for age, age^2, sex, education, and eTIV. For (a–d), residual volumes, VLT scores, and vocabulary scores are transformed to *z*-scores. CI, confidence interval; eTIV, estimated total intracranial volume; HsVol, hippocampal subfield volumetry; VLT, verbal list-learning test

consistently measurable in young adults (<35 years of age). We found that one supplementary word recalled was linked to a 0.6 mm^3 mean increase in CA1 volume, equivalent to a mean of 22,000 pyramidal neurons (Liagkouras et al., 2008) and 400 million synapses (Montero-Crespo et al., 2020). Thus, the best VLT performers could have, on average, approximately 500,000 pyramidal cells and 9 billion synapses more than the worst performers; this difference would make the relationship biologically plausible. We also observed that the VLT-CA1 volume relationship was independent of the meaning of words but was mediated by association-based mnemonics. The present explanation of the specific neuropsychological processes that underlie the relationship between the VLT–free recall performance and the hippocampal structure is a crucial new step in understanding the relationship between these two predictors of AD.

Clark et al. (2020) found little evidence that hippocampal gray matter volume was related to task performance in a healthy sample of 217 young adults. We also failed to find a relationship between VLT outcomes and the whole hippocampal volumes in either hemisphere. One critical difference between their study and ours is that Clark et al. (2020) ignored the structural and functional specificity of hippocampal subfields. Our results underscore the importance of examining the hippocampal subfield-level as others have already argued (Kesner & Rolls, 2015; La Joie et al., 2013; Maruszak & Thuret, 2014). The relation we found between VLT-free recall performance and the automatically segmented CA1 volume is consistent with previous studies using manual segmentation techniques (Mueller et al., 2011; Mueller et al., 2018); this consistency is an important consideration as long as there is no harmonized segmentation protocol for HsVol (Wisse et al., 2017). Our findings are also in agreement with studies implementing CA1 shape analyses (Costafreda et al., 2011; Novellino et al., 2018), suggesting reliability across structural methods. Here, we ensured the robustness of the results obtained in a cohort of 447 healthy young and middle-aged adults by collecting new data and applying similar methods to a second independent dataset of young adults under 35 years of age (National Academies of Sciences, Engineering, and Medicine, 2019). We were able to replicate the specific positive linear VLT-CA1 volume relationship in the second cohort of 1,242 healthy young adults. Interestingly, the results were the same despite some demographic and methodological differences between the two cohorts, that is, the proportion of women and right-handers, the visual versus auditory presentation of the items, the presence/absence of a 20-min delay between recalling trials, and the improvement of the segmentation method. Replication with these sample and method variations ensures the reliability of our observation in this population.

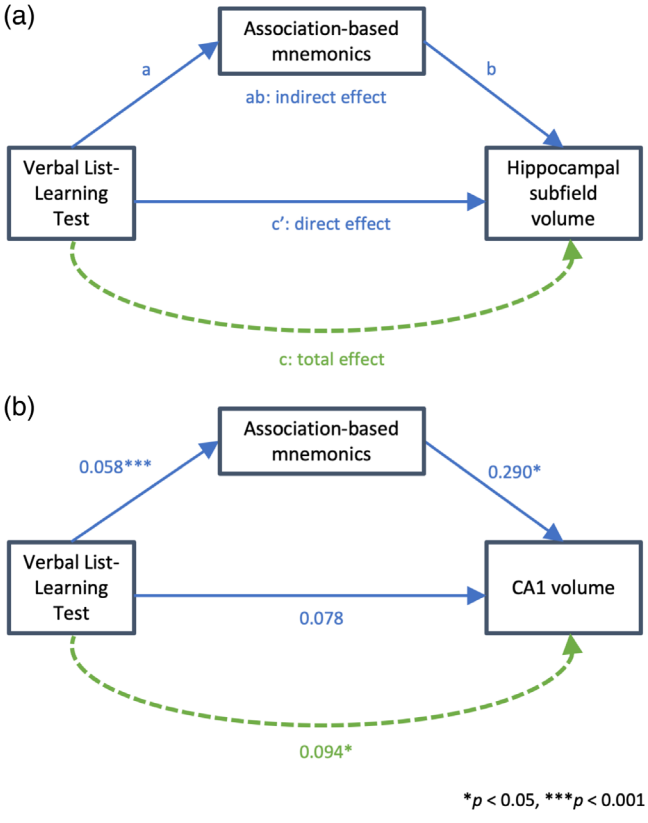

FIGURE 4 Mediation of the VLT–HsVol relationship by association-based mnemonics. (a) A schematic overview of paths decomposing the total effect (Path c) into direct (Path c') and indirect (Path ab) effects. (b) Bootstrapped mediation analyses in Sample 1 showed that association-based mnemonics mediated the VLT-CA1 volume relationship, ($p = .041$, $n = 444$). Standardized beta values are reported. HsVol, hippocampal subfield volumetry; VLT, verbal list-learning test

Verbal material to be learned is a prominent feature of VLTs. Authors who previously found a link between VLT performance and left CA1 volume often assumed that language-dependent processing explained the relationship (Aslaksen et al., 2018; de Toledo-Morrell et al., 2000; Zheng et al., 2018). Here, we did not observe any lateralization of the VLT-CA1 volume relationship, nor did we observe any link between CA1 volume and verbal intelligence assessed through a vocabulary test. Conversely, we found a link between CA1 volume and the pseudoword-LT, that is, the same learning protocol implemented with meaningless items. These results strongly suggest that the test design, rather than the meaning of the items, is responsible for the VLT-CA1 volume relationship. Assuming nonlanguage-specific processing is consistent with current theories stating that hippocampal representations serve as a basis for multiple cognitive processes (Murray, 2018; Olsen, Moses, Riggs, & Ryan, 2012), notably through their flexibility (Aly & Turk-Browne, 2018; Henke, 2010; Konkel, 2009; Rubin, Watson, Duff, & Cohen, 2014) and highly developed neocortical connectivity (Vogel et al., 2020).

VLT completion induces the use of association mnemonics based either on semantic or temporal (i.e., serial order) clustering (Cremona et al., 2020; Gross & Rebok, 2011; Worthen & Hunt, 2017). Here, we showed that the use of association-based mnemonics mediated the VLT–CA1 volume relationship, revealing that the best VLT performers used association-based mnemonics that positively correlated with CA1 volume. This preliminary result converges with previous knowledge on human CA1 functions. Indeed, the CA1 is involved in temporal and associative *relational memory* (i.e., the representation of arbitrary relations among the constituent elements of an event) (Jabès & Nelson, 2015) and *source memory* (associations between items and contexts) (Stevenson, Reagh, Chun, Murray, & Yassa, 2020). Functional MRI studies showed that CA1 representations of objects sharing a spatiotemporal context are more similar than those from different spatiotemporal contexts (Dimsdale-Zucker, Ritchey, Ekstrom, Yonelinas, & Ranganath, 2018) and that the CA1 contributes to the representations of sequences of ordered information (Chen, Morin, Parker, & Marsh, 2015). Interestingly, increases in oscillatory theta power (notably recorded in the CA1) are related to the semantic proximity of words to be processed, suggesting that a similar hippocampal computation represents the place, time, and semantic distance (Piai et al., 2016; Solomon, Lega, Sperling, & Kahana, 2019). It may be inferred that the CA1 plays an essential role in VLTs through its ability to represent both semantic and temporal links between items, potentially explaining the relationship between its volume and the individual difference in the VLT-free recall performance.

Finally, we did not observe any relation between VLT-free recall performance and the five other hippocampal subfields studied (i.e., CA3, CA4, DG, presubiculum, and subiculum). The lack of relation between the presubiculum and subiculum volumes and the VLT-free recall performance in healthy young and middle-aged adults is consistent with our literature review (see Supporting Information). Regarding CA3, its smallest volume (180–260 mm^3) may explain our negative result that could have been caused by a lack of sensitivity of the segmentation technique (Sämann et al., 2020). Another limitation concerns the CA4-DG subfields, located in the internal bends of the hippocampus, whose volumes must be interpreted with caution, as stated by the Freesurfer providers (Iglesias et al., 2015).

5 | CONCLUSIONS

Subfield-level volumetry revealed a positive correlation between VLT-free recall performance and CA1 volume in healthy young and middle-aged adults, and demonstrated the improved sensitivity of this approach relative to the whole hippocampal approach. Replication on a large independent sample of young adults showed identical patterns of relationships, demonstrating the high reliability and robustness of our findings. Exploratory analyses revealed that the VLT–CA1 volume relationship is mediated by the use of association-based mnemonics, suggesting that the construction of association-based representations required to perform VLTs could explain the link between VLT performance and hippocampal CA1 volume. Our results encourage further research on the relation between VLT outcomes and HsVol, particularly how specific relationship profiles may

emerge according to age and health status. Understanding the neurocognitive processes, underpinning such age- or disease-dependent profiles can help create neuropsychological markers of hippocampal integrity that are less invasive and more affordable than imaging-based biomarkers. Given the spread and severity of neurodegenerative diseases linked to hippocampal dysfunction, with AD in the foreground, optimized cognitive markers would be valuable tools for the early detection of individual vulnerabilities (Cerami et al., 2017; Weissberger et al., 2017).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Sandrine Cremona: Conceptualization, methodology, formal analysis, validation, visualization, writing—original draft, and writing—review & editing. **Laure Zago:** Conceptualization, investigation, methodology, and writing—review & editing. **Emmanuel Mellet:** Methodology, investigation, and writing—review & editing. **Laurent Petit:** Writing—review & editing. **Alexandre Laurent, Antonietta Pepe**: Software. **Ami Tsuchida**: Software and writing—review & editing. **Naka Beguedou**: Investigation and validation. **Marc Joliot**: Investigation, methodology, and writing—review & editing. **Christophe Tzourio:** Writing—review & editing, project administration, and funding acquisition. **Bernard Mazoyer:** Investigation, writing—reviews & editing, project administration, and funding acquisition. **Fabrice Crivello:** Conceptualization, methodology, and writing—review & editing.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are not publicly available, as they contain information that could compromise research participant consent (i-Share & MRi-Share) and that is copyrighted (BIL & GIN). However, data are available from the corresponding author [SC] upon reasonable request and with permission of the principal investigators of the cohorts [BM or CT].

ETHICS STATEMENT

Participant data for this study were acquired from two cohorts in respect with the guidelines of the Declaration of Helsinki: (a) BIL & GIN: study protocol approved by the Basse-Normandie Ethics Committee. (b) i-Share-MRi-Share: study protocol approved by the French National Commission of Informatics and Liberties and the Bordeaux CPP SOMIII Ethics Committee.

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