A hippocampal-anterior thalamic circuit associated with learning rate in ageing

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Abstract

Memory normally declines with ageing and these age-related cognitive changes are associated with changes in brain structure. Episodic memory retrieval has been widely studied during ageing, whereas learning has received less attention. Here we examined the neural correlates of learning rate in ageing. Our study sample consisted of 982 cognitively healthy female and male older participants from the Vallecas Project cohort, without a clinical diagnosis of mild cognitive impairment or dementia. The learning rate across three consecutive verbal memory (Free and Cued Selective Reminding Test) recall trials was used as a predictor of grey matter (GM) and white matter (WM) volume using voxel-based morphometry, and WM microstructure using tract-based spatial statistics on fractional anisotropy (FA) and mean diffusivity (MD) measures. Immediate recall improved by 1.4 items per trial on average, and this learning rate was faster in women and negatively associated with age. Structurally, hippocampal and anterior thalamic GM volume correlated positively with learning rate. Learning also correlated with the integrity of WM microstructure (high FA and low MD) in an extensive network of tracts including bilateral anterior thalamic radiation, fornix, and long-range tracts. These results suggest that structural GM and WM characteristics, centred on a hippocampal-anterior thalamic circuit, support learning capacity in ageing. Specifically, reduced volume and microstructure may explain some of the age-related memory deficits that result from impaired learning.

Significance statement

A detailed understanding of age-related memory changes is crucial in an increasingly ageing population, in which memory decline is prevalent. Whilst memory performance is usually quantified by the ability to correctly retrieve information, memory impairment could be caused by a reduced ability to learn or encode information. In a cohort of cognitively healthy ageing participants, we found an association between verbal learning rate and grey matter volume and white matter microstructure in the limbic system. These findings establish the

neural underpinnings of the often-overlooked learning phase of the memory process and have important implications for our understanding of neurobiological changes in healthy ageing and their cognitive phenotypes.

Introduction

Ageing is accompanied by a decline in cognition, most characteristically in memory performance (Glisky, 2007). Memory impairments in ageing can manifest in different ways, therefore providing insight into different structural and functional age-related changes. Furthermore, exploring the neural underpinnings of these various manifestations (e.g., learning versus retention) could inform dissociations between normal age-related decline and decline driven by neurodegenerative diseases such as dementia. Memory encapsulates encoding, consolidation and retrieval processes, and deficits in either three may affect performance independently. Memory decline in ageing is often measured in terms of retention, however, impairments could also be driven by a diminished ability to learn information, rather than to retrieve it. We therefore aimed to elucidate the structural brain properties underlying learning rate in ageing.

Ageing has been associated with a global reduction in grey matter (GM) volume (Grieve et al., 2007; Farokhian et al., 2017), although to different extents across brain regions (Cox et al., 2018). Numerous studies have found a specific GM volume loss in prefrontal, temporal and parietal cortices (Elliott, 2020; Cox et al., 2021), associated with general cognitive and memory-specific decline (Gorbach et al., 2017; Cox et al., 2021). White matter (WM) age-related changes in fractional anisotropy (FA) and mean diffusivity (MD), have also been reported (Bennett et al., 2010; Madden and Parks, 2017). FA and MD are negatively correlated such that reduced WM integrity is indexed by a decrease in FA and an increase in MD. Like GM, age-related WM changes are apparent throughout the brain (Grieve et al., 2007; Farokhian et al., 2017), although with greater effects in anterior than posterior tracts

(Bennett et al., 2010). Whilst these structural changes contribute to our understanding of brain ageing, it is vital to also consider their cognitive correlates.

A commonly observed form of age-related cognitive decline is impaired memory, which has been associated with reduced hippocampal volume (Persson et al., 2012; Hedden et al., 2016; Gorbach et al., 2017), as well as with damage to the microstructure of frontal and temporal WM tracts (de Mooij et al., 2018; Rizvi et al., 2020), and specifically limbic tracts (Bennett et al., 2015). Furthermore, recognition performance on neuropsychological episodic memory tests has been shown to correlate with FA and MD measures in the fornix, cingulum, and superior and inferior longitudinal fasciculi (Sasson et al., 2013). However, other studies have not found correlations between WM microstructure and episodic retrieval in ageing (Salami et al., 2012; Laukka et al., 2013; Gorbach et al., 2017).

Learning, which is potentially dissociable from retrieval processes (Kwok and Buckley, 2010; Bennett et al., 2015), is often overlooked in the context of ageing. Whilst memory performance is usually quantified by the ability to correctly recognise or recall information, a retrieval impairment could be caused by reduced ability to learn information. Indeed, there is evidence for reduced error-driven (Nassar et al., 2016) and probabilistic learning (Samanez-Larkin et al., 2012; Herff et al., 2020) in older adults, but evidence for similar deficits in episodic learning is lacking. Relatedly, the microstructure of WM limbic tracts has been related to episodic and navigational learning across species (Aggleton et al., 1995; Buckley et al., 2008; Hofstetter et al., 2013; Hodgetts et al., 2020), but it is still unclear whether such changes in these tracts can explain memory deficits in ageing.

We investigated whether the learning rate in the Free and Cued Selective Reminding Test (FCSRT) is associated with age as well as its neural manifestation in GM and WM volume and WM tract microstructure. In a large cross-sectional cohort of healthy older adults, we first calculated the learning rate across three FCSRT trials (i.e., how many additional words are successfully encoded in each trial) and tested for an association with age. To examine

brain-cognition associations, we used learning rate as a predictor to examine 1) GM and WM volume using voxel-based morphometry (VBM), and 2) WM microstructure using tract-based spatial statistics on FA and MD measures. Given the critical role of hippocampus in episodic memory and correlation with structural changes in ageing, we hypothesised that hippocampal GM volume, and associated WM limbic tract microstructure would correlate with learning rate.

Methods

Participants. All participants in this study were part of the Vallecas Project, a single-centre longitudinal study with annual visits. Inclusion and exclusion criteria for participants in this project have been described elsewhere (Olazarán et al., 2015). From this cohort, data from the baseline visit of 982 cognitively normal participants (mean age = 74.8, SD = 3.9, 637 (64.9%) females) were included in the current study. Any subject with a diagnosis of mild cognitive impairment or Alzheimer's disease at this first visit was excluded. All participants provided written informed consent and the Vallecas Project was approved by the Ethics committee of the Instituto de Salud Carlos III.

Neuropsychological assessment. Participants completed a battery of neuropsychological assessments as part of the Vallecas Project protocol. In this study we reported the total score of the Mini Mental State Examination (MMSE; Folstein et al., 1975) and we mainly focused on the Free and Cued Selective Reminding Test (FCSRT; Buschke, 1984), assessing learning and retention of verbal memory, with immediate and delayed recall components. The test was administered using standard procedures (Peña-Casanova et al., 2009). During the study phase, participants were shown a card with four words and asked to identify the word corresponding to a specific category, cycling through all four words, on four different cards (16 words in total). Following the study phase, three recall trials were used for the learned items (immediate recall), each one followed by 20 seconds of interference counting backwards. The same procedure was done after a 30-minute delay (delayed

recall). To assess the learning rate across trials, we fit a linear-mixed effects model of the number of items recalled in each trial, as a function of the recall trial (first, second, and third) using the *lme4* package in R 4.0.2 (https://www.r-project.org/). The model also included a random slope of the recall trial, and a random intercept per participant, capturing inter-individual variability in learning rate (across the three trials). The learning rate coefficient for each participant was extracted for subsequent analyses. Next we built a multiple regression model where the learning rate was the dependent variable, sex, age and level of education were the predictors, and delayed free recall score of the FCSRT was included as a covariate to rule out the retrieval phase of the memory process.

MRI Data acquisition. Images were acquired using a 3T MRI (Signa HDxt GE) with a phased array eight-channel head coil. T1-weighted images (3D fast spoiled gradient echo with inversion recovery preparation) were collected using a repetition time (TR) of 10ms, echo time (TE) of 4.5ms, field of view (FOV) of 240mm and a matrix size of 288x288 with slice thickness of 1mm, yielding a voxel size of 0.5 x 0.5 x 1 mm^3. Diffusion-weighted images were single-shot spin echo echo-planar imaging (SE-EPI), with TR 9200ms, TE 80ms, b-value 800s/mm^2 and 21 gradient directions, FOV 240mm and matrix size 128 x 128 with slice thickness of 3mm.

Grey and white matter VBM. The analysis was carried out in SPM12 (version r6225; https://www.fil.ion.ucl.ac.uk/spm). T1-weighted images were segmented into grey matter, white matter and cerebrospinal fluid and then aligned and normalised to MNI space using the DARTEL algorithm (Ashburner, 2007). Prior to statistical modelling, the normalised images were smoothed using a 6mm FWHM Gaussian kernel. The pre-processed grey and white matter maps were entered into separate general linear models (GLM) with learning rate from the memory task as the predictor of interest, and total intracranial volume (TIV), sex, and the delayed free recall score of the FCSRT as covariates. Age and education were not used in the model as additional covariates, because they are correlated with FCSRT delayed free recall so the effects of age and level of education are already accounted for by

FCSRT delayed free recall. We conducted whole-brain analyses using a threshold-free cluster enhancement (TFCE) approach with 5000 permutations and default parameters (E = 0.5 and H = 2) using the TFCE tool (version r223) for CAT12 toolbox in SPM (http://dbm.neuro.uni-jena.de/tfce). The AAL3 atlas neuroanatomical labels were used to describe neuroanatomical loci (Rolls et al., 2020) and Mango software was used to produce the figure (http://rii.uthscsa.edu/mango/). These analyses assessed which regions were positively associated with the immediate recall learning slope. Significant results are reported at a family-wise error (FWE) corrected level of $p < 0.05$.

White matter tract-based spatial statistics (TBSS). Of the 982 participants, seven were excluded as they did not have diffusion data. For preprocessing these images, the FSL toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki) was used for motion and eddy current correction, the extraction of non-brain voxels and, lastly, the calculation of voxel-wise diffusion maps (FA and MD) for each participant. Individual FA and MD maps were then used in the FSL TBSS pipeline (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuider), detailed methods described by Smith et al. (2006). The general outline of the process is 1) FA individual maps were non-linearly registered to standard space (FMRIB58_FA template) (Andersson et al., 2007); 2) a mean FA image was created by averaging all co-registered FA maps; and 3) individually aligned images were projected onto the mean FA skeleton—representing the centers of all tracts common to the study sample—and skeletonized images were used for voxel-wise analysis. Diffusivity maps for MD were generated by applying the same steps detailed above. The same GLM design matrix as the VBM analysis was used along with the TFCE approach with 5000 permutations (default parameters E = 0.5 and H = 2). Significant results are reported at a family-wise error (FWE) corrected level of $p < 0.05$. To visualise our TBSS results we used the multimodal analysis and visualisation tool (MMVT; Felsenstein et al., 2019). The pipeline follows these steps: 1) Binary masking: all the voxels in the TBSS volume below the threshold (0.95) were set to zero. 2) Outlier voxels removal using the Open3D python package (Zhou et al., 2018). 3) Smoothing the volumetric data using a 3D

Gaussian filter (Virtanen et al., 2020). 4) Surface creation from the volume's TBSS surfaces using the marching cubes algorithm (Lorensen and Cline, 1987). For that, we re-calculate the threshold to give us the same number of voxels after the smoothing step. 5) Translation for the surfaces' vertices coordinates. 6) Projection of the volumetric data on the surfaces.

Results

Memory and neuropsychological performance

On average, across three trials, participants correctly remembered 7.9 items (SD = 2.6). When looking at individual trials, performance improved as trials progressed, reflecting a positive learning slope (see **Table 1** for number of items recalled, and **Figure 1A** for learning rates). Our linear model predicting the learning rate as a function of age, sex, and level of education revealed significant effects of the three predictors after correcting for FCSRT delayed free recall score. Learning rate and delayed free recall FCSRT are positively correlated (Pearson's r = 0.7; $p < 2.2\times10^{-16}$). Age has a negative effect on learning rate (F(1,965) = 10.45, p = 0.001) (**Figure 1B**), sex also has an effect (F(1,965) = 4.66, p = 0.031) and being a woman is positively associated with learning rate (**Figure 1C**). Finally, having a higher level of education is positively associated with learning rate (F(3,965) = 5.17 , p < 0.002) (**Figure 1D**). There is no significant interaction between the three predictors (age, sex and years of education).

	Total sample (n = 982) Mean (SD)	**Women** (n = 637) Mean (SD)	**Men** (n = 345) Mean (SD)
Demographics			
Age, years	74.8 (3.9)	74.8 (3.9)	74.8 (3.9)

Levels of education, count (%)	Less than primary	185 (18.8)	137 (21.5)	48 (13.9)
	Primary	295 (30.0)	222 (34.9)	73 (21.1)
	Secondary	245 (24.9)	151 (23.7)	94 (27.2)
	Higher education	257 (26.2)	127 (19.9)	130 (37.7)
Neuropsychological performance				
MMSE, total score		28.6 (1.6)	28.6 (1.6)	28.7 (1.4)
Trial 1 immediate free recall FCSRT, items recalled		6.5 (2.1)	6.7 (2.1)	6.3 (2.1)
Trial 2 immediate free recall FCSRT, items recalled		7.9 (2.4)	7.9 (2.4)	7.8 (2.4)
Trial 3 immediate free recall FCSRT, items recalled		9.2 (2.5)	9.4 (2.6)	9.0 (2.6)
Learning rate immediate free recall FCSRT, items recalled/trial		1.4 (0.3)	1.4 (0.3)	1.3 (0.3)
Delayed free recall FCSRT, items recalled		9.4 (2.6)	9.5 (2.7)	9.3 (2.6)

Table 1. Demographic and neuropsychological profile of the total sample and split by sex. MMSE: Mini Mental State Examination total score, FCSRT: Free and Cued Selective Reminding Test.

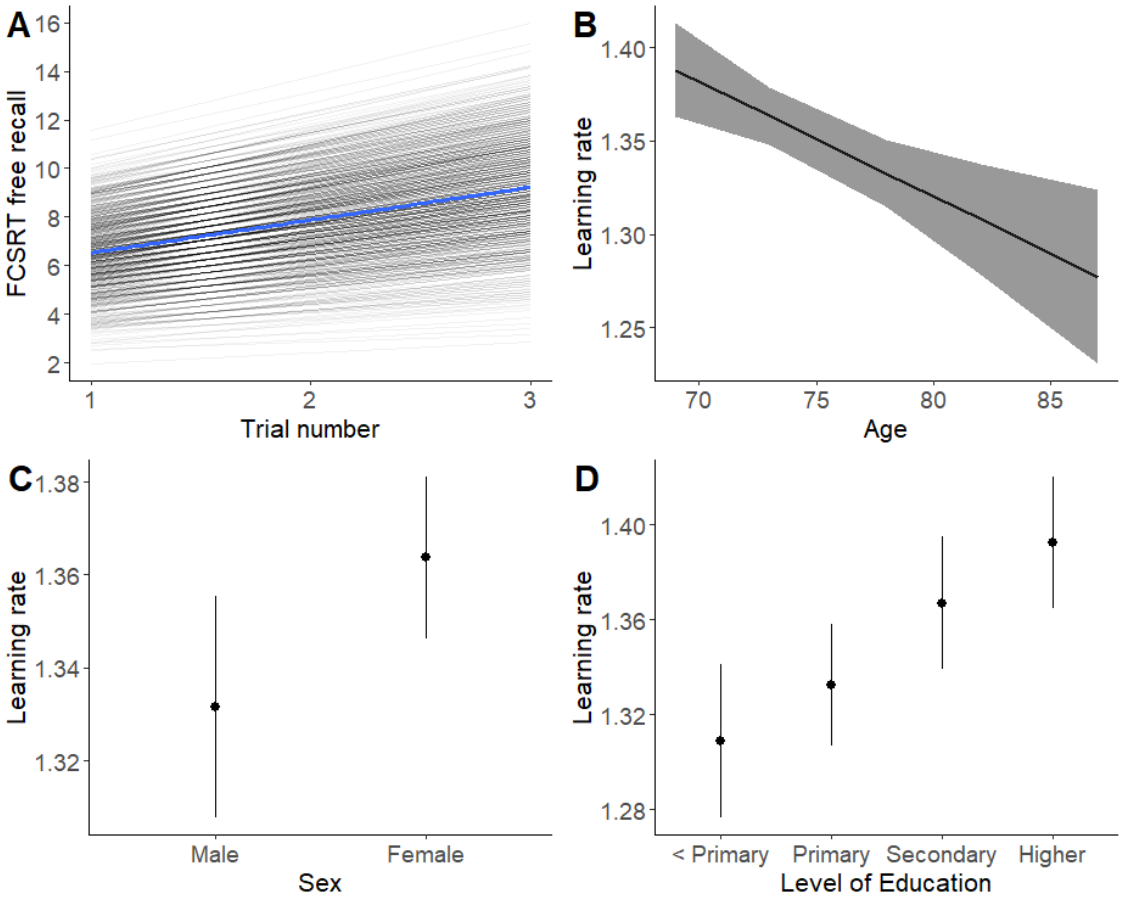

Figure 1. Learning rates across FCSRT trials are related to age, sex and level of education. A Mean and individual learning rates across the three free immediate recall FCSRT trials. After controlling for the rest of the model predictors, **B** learning rate decreases with age, **C** females learn faster than males and **D** level of education is positively associated with learning rate. Error bars represent 95% confidence intervals.

Grey and white matter volume (VBM)

We found a positive correlation between learning slope and grey matter volume in the bilateral hippocampus, with more pronounced effects on the left side (**Figure 2A**), and the right anterior thalamic nucleus with some extension to adjacent nuclei (right ventroanterior and ventrolateral thalamic nuclei) (**Figure 2B**, **Table 2-1**). There were no significant associations between learning rate and white matter volume (data not shown).

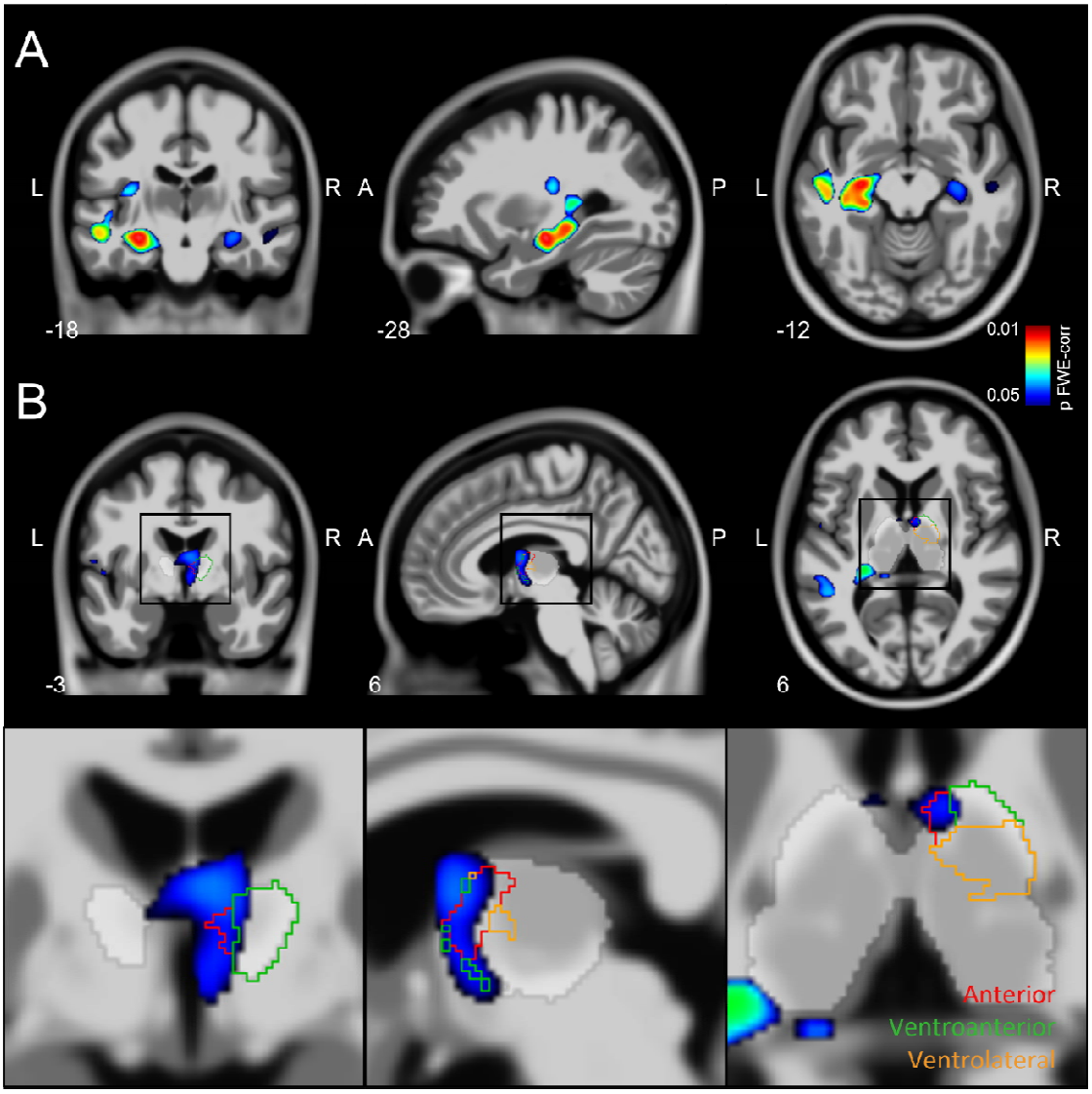

Figure 2. Grey matter volume of hippocampal-anterior thalamic circuit correlates with learning rate in the older adults. The positive correlation has been overlaid on a canonical T1 image (thresholded at $p < 0.05$ FWE-corr) to show a significant effect in **A** hippocampus bilaterally and **B** right anterior (red), ventroanterior (green) and ventrolateral thalamic nuclei (orange) (thalamic ROIs in the inset come from the AAL3 atlas (Rolls et al., 2020). The coordinates of the sections are given in mm. L: left, R: right, A: anterior, P: posterior.

White matter microstructure (TBSS)

We first examined FA as a marker of WM integrity. We found a bilateral network of temporal, parietal and occipital tracts showing a positive association with learning rate. Among tracts showing significant positive correlations were the bilateral anterior thalamic radiation (ATR), fornix, inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate (**Figure 3A-B, Table 3-1**). Next, we examined MD and found a negative association between a similar network of bilateral tracts and FCSRT learning rate, including bilateral ATR, corticospinal tract, forceps major and minor, cingulum (cingulate), IFOF, ILF, SLF, uncinate and fornix (**Figure 3C-D, Table 3-1**).

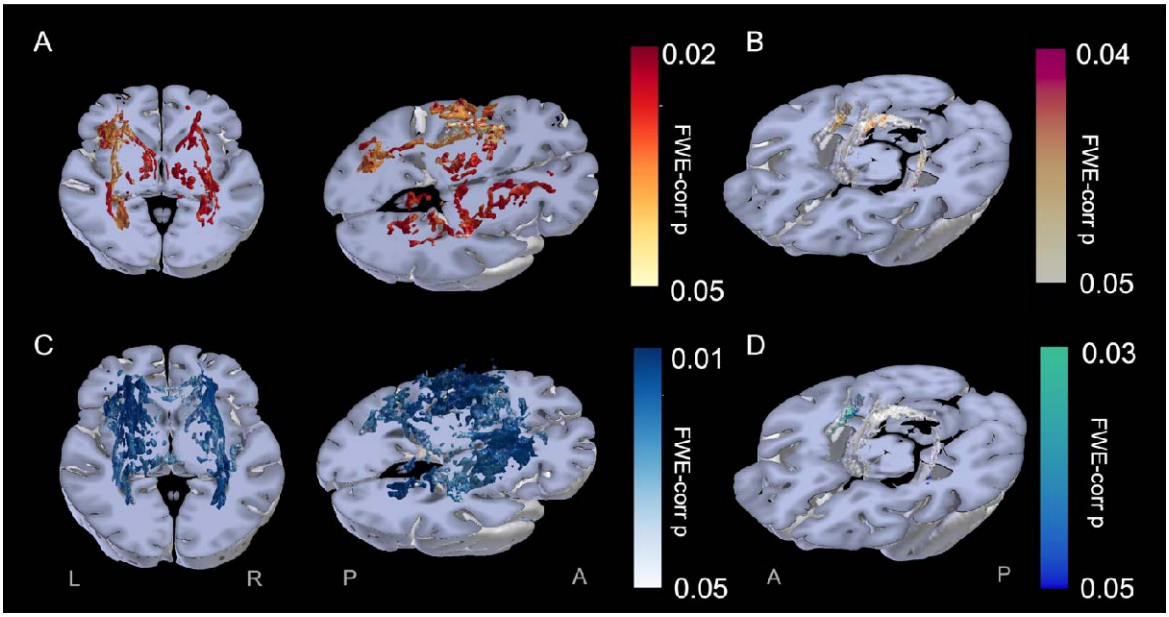

Figure 3. Extensive network of white matter microstructure integrity is related to learning rate in the older adults. A. Positive correlation between FA and learning rate (warm colours; $p < 0.05$ FWE-corr). **B.** FA effects overlaid on the fornix. **C.** Negative correlation between MD and learning rate (cold colours; $p < 0.05$ FWE-corr). **D.** MD effect overlaid on the fornix.

Discussion

Learning rate is faster in women, declines with age and is associated with neuroanatomical structural properties. We found a positive correlation between GM volume and learning rate, where participants with greater hippocampal and anterior thalamic nucleus volume learned at a faster rate than those with reduced volume. Furthermore, we found that FA was positively associated with learning rate in an extended network including limbic tracts, indicating that structural integrity of these tracts indexed learning ability. A complementary negative association was observed for MD, in similar tracts, such that increased MD was associated with a slower learning rate. These findings suggest that structural properties of hippocampal-anterior thalamic circuit contribute to learning ability in ageing. Specifically, reduction in volume and WM microstructure may explain some age-related memory deficits stemming from slower learning, as opposed to deficits in consolidation or retrieval.

Previous research on neural substrates of cognitive decline in ageing has shown a hippocampal volume deterioration with age that correlated with memory performance (Persson et al., 2012; Hedden et al., 2016; Gorbach et al., 2017). The more pronounced effect we observed in the left hippocampus is in accordance with previous VBM findings of verbal memory tasks (Ezzati et al., 2016), and the general lateralisation of verbal functions. Our results therefore extend previous research on the relationship between hippocampal volume and memory decline in ageing, showing learning ability is also indexed by hippocampal volume. Note that it is unlikely that these effects reflect memory function in general, given that delayed free recall was included as a covariate in our model.

Structural properties of extra-hippocampal limbic regions were also associated with learning ability. Our GM thalamic findings indicate a correlation between learning rate and the right anterior thalamic nucleus, extending to right ventroanterior and right ventrolateral nuclei. The anterior thalamic nuclei have been suggested to play an important role in learning and memory (Winocur, 1985; Aggleton et al., 2010), beyond navigation (Wolff and Vann, 2019;

Nelson, 2021). Specifically, and in line with our results, Leszczyński and Staudigl (2016) posited that the anterior thalamus might modulate information flow, via attention allocation, to support learning. Taken together with increased hippocampal volume related to better learning rate, our results indicate that the limbic system plays an important role in learning ability in ageing, and might explain some of the impairments in navigating in a novel environment (Grzeschik et al., 2021), and impaired learning strategies observed in MCI (Ribeiro et al., 2007)The fornix is a major hippocampal input/output pathway and has been associated with visuo-spatial learning across species (Buckley et al., 2008; Hofstetter et al., 2013; Hodgetts et al., 2020). The fornix links the hippocampus with the anterior thalamic nuclei (via mammillary bodies), with both regions showing grey matter volume relationship with learning rate. Furthermore, we found that fornix integrity, as captured by bilateral FA and MD, correlated with learning rate in older adults. This finding suggests that the fornix also plays a role in verbal episodic learning, as captured in our study. We also found that the WM integrity of the ATR was correlated with learning rate. The ATR, which connects the anterior and dorsomedial thalamus with the prefrontal cortex (Grodd et al., 2020), may play a role in learning (McGuire et al., 2014).

In addition to changes in limbic GM volume and WM microstructure, we found learning rate was associated with broader changes within bilateral WM tracts connecting occipital-temporal-frontal regions (ILF, SLF, IFOF). This result might point toward an overall WM microstructure effect, as previously noted in age-related cognitive decline (Grieve et al., 2007; Farokhian et al., 2017; de Mooij et al., 2018; Rizvi et al., 2020; Molloy et al., 2021). Importantly, given that we control for age differences by inclusion of the delayed free recall score as a covariate in the regression model, this result cannot be attributed to age differences in our cross-sectional cohort. With respect to specific cognitive functions, ILF and SLF have been shown to relate to memory performance in normal ageing (Sasson et al., 2013). ILF and IFOF facilitate flow of visual information up the visual stream (Rokem et al., 2017), and IFOF has been associated with semantic processing (Duffau, 2008), potentially

supporting learning performance in our task. Therefore, the observed relationship between microstructure of these tracts and learning ability might reflect a more general aspect of cognitive ability. Whilst we found significant correlations between learning rate and FA and MD, no correlations were found for WM volume, potentially due to reduced sensitivity of WM volume to age-related decline (Wozniak and Lim, 2006).

Finally, it is important to note some limitations of the current study; we analysed data from a cross-sectional cohort of healthy older adults. As GM and WM properties and memory function both deteriorate with age, future longitudinal studies would be needed to better understand the relationship between learning ability and structural changes as ageing progresses and eliminate age-related confounds in cross-sectional studies (Elliott, 2020). We used the learning rate across trials in an established neuropsychological memory task (FCSRT) as a measure for episodic learning; it would be interesting to examine neural correlates of other forms of learning such as error-driven and statistical learning (Samanez-Larkin et al., 2012; Nassar et al., 2016; Herff et al., 2020), as well as consider learning ability as a potential cognitive phenotype in pathological ageing.

In conclusion, in a cross-sectional cohort of healthy older adults, we found learning rate on the FCSRT task was positively associated with GM and WM structural changes in the limbic system, including the hippocampus, fornix and anterior thalamic nucleus. Furthermore, there was a positive correlation between learning rate and long-range WM tracts (ILF, SLF, IFOF). Our findings suggest that some age-related memory deficits might be caused due to impaired learning underpinned by such structural change.

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