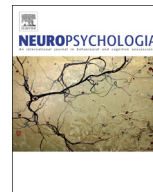




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White matter integrity in brain structures supporting semantic processing is associated with value-directed remembering in older adults

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ARTICLE INFO

Keywords:

Diffusion tensor imaging

Aging

Value

Reward

Memory

Semantic

ABSTRACT

White matter microstructure changes substantially in aging. To better understand how the integrity of white matter structures supports the selective learning of rewarding material, 23 healthy older adults were tested on a value-directed remembering task. This task involved successive free recall word lists where items differed in importance, as denoted by value cues preceding each word. White matter structure was measured using diffusion tensor imaging (DTI). We found that greater structural integrity (as measured by lower mean diffusivity) in left inferior fronto-occipital fasciculus was associated with greater recall for high-value items, but not low-value items. Older adults with greater structural integrity in a tract involved in semantic processing are thus able to more successfully encode high-value items for subsequent recall. However, unlike prior findings in younger adults, older adults' memory for high value-items was not significantly correlated with the structural integrity of the uncinate fasciculus, nor with the strength of anatomical connectedness between the bilateral nucleus accumbens to ventral tegmental area reward pathway. These structural imaging findings add support to recent functional neuroimaging demonstrations that value-related modulation of memory in older adults depends heavily on brain circuits implicated in controlled processing of semantic knowledge.

Throughout life, we are presented with more information than we can remember. In order to be efficient learners, we must selectively encode what is most valuable. One way to examine the degree to which an individual is engaged in selective learning is through the value-directed remembering (VDR) paradigm. In this task, items are paired with point-values that are earned with later retrieval, and the subject's goal is to earn a high score (Castel et al., 2002). These point-values simulate presented information differing in importance. A wide literature shows that the encoding and retrieval of various stimuli is enhanced when items are paired with a high point-value or monetary value (Adcock et al., 2006; Ariel et al., 2015; Carter, 2009; Cohen et al., 2014), and that this value-related selectivity is often intact in normal healthy aging (Castel et al., 2009; Castel et al., 2002; Cohen et al., 2016; Spaniol et al., 2013; see Geddes et al., 2018, for a counterexample). Although the use of point-values in VDR research does not provide participants with tangible rewards, the above research shows that these value cues are highly effective in motivating selective learning; additionally, both point-values and monetary values similarly elicit activity in reward-related regions in the midbrain and ventral striatum (Cohen et al.,

2014).

Multiple cognitive and neural mechanisms are theorized to underlie the strengthening of memories for high-value items. For one, value cues have been shown to elicit activation in a reward circuit, including the nucleus accumbens (NAcc) and ventral tegmental area (VTA), that is thought to represent anticipation of future rewards and that may influence goal-directed motivation (Adcock et al., 2006; Carter, 2009; Cohen et al., 2014). The VTA has been shown to modulate long-term potentiation in the hippocampus through its dopaminergic connections (Bethus et al., 2010; Rossato et al., 2009), and the NAcc, VTA, prefrontal cortex (PFC), hippocampus, and subiculum are theorized to form a loop that regulates goal-directed learning (see Lisman and Grace, 2005 for a review). However, some research has failed to find an increase in activity in reward-related regions for older adults during or prior to encoding of high-value items (Cohen et al., 2016; Geddes et al., 2018). While Geddes et al. (2018) found no reward-related enhancement of memory, Cohen et al. (2016) reported a robust effect of value on older adults' behavioral memory measure despite the apparent lack of involvement of the dopaminergic reward system. Cohen et al. (2016)

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<https://doi.org/10.1016/j.neuropsychologia.2019.04.003>

Received 6 October 2018; Received in revised form 28 February 2019; Accepted 11 April 2019

Available online 12 April 2019

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also found fMRI evidence that an alternate brain mechanism, in place of reward-system upregulation, could account for maintained value-related encoding selectivity in older adults.

An additional mechanism that seems to contribute to VDR in both younger adults and older adults is strategy-driven differences in encoding based on value. In both age groups, Cohen et al. (2014, 2016) observed increased activity in brain regions related to semantic processing, including left ventrolateral prefrontal cortex and left posterior lateral temporal cortex, during encoding of high-value information. Additionally, the magnitude of this increase in activity correlated with a selectivity index (i.e. the degree to which high-value items were preferentially recalled over low-value items) in both younger and older adults. This preserved ability to selectively engage semantic strategies during encoding was interpreted to underlie older adults' preserved ability to preferentially encode high-value items in the VDR task. Other studies have further explored participants' ability to selectively attend to high-value items (Ariel et al., 2015; Robison and Unsworth, 2017) and use more effective learning strategies that involve associative and semantic processing (Ariel et al., 2015; Cohen et al., 2017). These learning strategies are thought to produce a deeper and more elaborative encoding of semantic information that has been shown to improve memory performance (Craig and Tulving, 1975; Richardson, 1998). During encoding, participants commonly report using more elaborative strategies such as mental imagery, putting items in a sentence, or thinking about the relationship between items (Cohen et al., 2016; Ariel et al., 2015). Value selectivity and task performance are enhanced when participants report actively ignoring low-value items (Ariel et al., 2015), and instructing participants to use this strategy improves performance (Robison and Unsworth, 2017).

In the present study, we used diffusion tensor imaging (DTI) to measure white matter characteristics along pathways that we hypothesized to be important in value-directed remembering for healthy older adults; primary tracts of interest were the left inferior fronto-occipital fasciculus (IFOF) and the left uncinate fasciculus (UF). Fractional anisotropy (FA) in left UF correlated with the number of high-value items recalled in the young adult comparison sample of the present dataset (Reggente et al., 2018). There was not clear evidence to support a relationship between IFOF FA and recall in our young adult dataset, but there was still a strong a priori basis to believe that this tract may be relevant to successful encoding in a verbal learning task, as is discussed below.

The IFOF pathway extends ventrally from the orbitofrontal cortex to ventral occipital cortex (Catani and Thiebautdeschotten, 2008), with terminations in posterior orbital cortex, temporal-basal cortex, and the superior parietal lobule (Duffau et al., 2013; Martino et al., 2009). Duffau et al. (2013) proposed that the IFOF is a crucial pathway whereby visual information processed in occipital and temporal-basal associative cortices, and auditory information processing in temporal and parietal associative cortices, is fed directly to prefrontal cortex allowing for top down control of this semantic information. This semantic network appears to be largely left-lateralized (de Zubicaray et al., 2011; see Patterson et al., 2007 for a review), particularly when supporting the encoding and retrieval of verbal stimuli (Rice et al., 2015). The IFOF has been shown in prior DTI studies to be involved in both the retrieval (de Zubicaray et al., 2011) and control of semantic information (Nugiel et al., 2016), a conclusion further supported by lesion research (Harvey and Schnur, 2015) and examinations of functional connectivity (Turken and Dronkers, 2011). Additionally, many of the brain regions showing increased activity during encoding of high-value items in the present task, relative to encoding of low-value items, are connected via the IFOF. These regions include portions of left lateral PFC, left posterior lateral temporal cortex, and bilateral occipital cortex (Cohen et al., 2016). Given these functional and anatomical findings, it seemed likely that left IFOF would be involved in older adults' encoding of high-value words. In order to limit our number of comparisons, and because this semantic network is left-lateralized (e.g., de Zubicaray

et al., 2011), we decided to focus on left hemisphere tracts.

We also examined whether integrity of the left uncinate fasciculus (UF) would be associated with memory for high-value items, a result that would replicate findings from our young adult sample (Reggente et al., 2018). The UF connects the anterior temporal lobe, which is involved in domain-general semantic processing (Chen et al., 2017; Patterson et al., 2007), with the medial and lateral orbitofrontal cortex (Catani and Thiebautdeschotten, 2008), which is involved in goal-directed learning and retrieval search (Dobbins and Wagner, 2005). White matter integrity in the UF is related to episodic memory (Lockhart et al., 2012), and like the IFOF, the UF has been associated with semantic processing (Matsuo et al., 2008; McDonald et al., 2008; Acosta-Cabronero et al., 2011; de Zubicaray et al., 2011; Galantucci et al., 2011). Thus, we expected that white matter connections instantiated in either IFOF or UF could be important to semantic processing, and therefore to effective encoding of high-value words in older adults.

Finally, the likelihood of white matter emanating from the NAcc and reaching the VTA—a proxy measure of anatomical connectedness from one ROI to another—was examined. These reward regions are part of a goal-directed loop that modulates learning (Lisman and Grace, 2005), and they have been shown to be robustly connected (Krebs et al., 2011; Morales and Margolis, 2017). In a recent DTI study using a probabilistic learning task, older adults who performed comparably to younger adults had the greatest structural connectivity between NAcc and VTA, and this connectivity was related to improved value representation in NAcc (Chowdhury et al., 2013). Furthermore, Reggente et al. (2018) found that the robustness of this pathway was correlated with greater memory selectivity and increased recall for high value words in a sample of young adults performing the same VDR task as that used in the present study. However, given that older adults showed less value-induced modulation of activity in these reward-related regions during encoding (Cohen et al., 2016), we anticipated that the structural integrity of this pathway might not support memory for high-value items in older adults in the same way that it does in younger adults. Although the present study was designed to examine individual differences in older adults, younger adult data from Reggente et al. (2018) were also re-analyzed to facilitate age group comparisons.

1. Methods

1.1. Participants

Data from 25 older adults were collected for this study. Participants were recruited using flyers posted at the UCLA Medical Center and flyers and newsletter postings in West Los Angeles and the San Fernando Valley. Data from two participants were excluded from analysis due to neurological abnormalities observed in their MRI data (one cavernoma, one meningioma). The final sample of 23 older adults had an age range of 60–80 years ($M = 68.7$, $SD = 5.7$), and included 13 women and 10 men. These participants were all right-handed native English speakers with normal or corrected to normal vision. All participants scored at least 27 on an adaptation of the Mini-Mental State Exam (Folstein et al., 1975) indicating that they did not show major signs of dementia. Additionally, none of these participants had substantial neurological abnormality, as observed in their anatomical MRI scans, and none of them reported currently taking psychoactive medication for a psychiatric or neurological disorder. Informed consent was obtained and the study was run according to the guidelines of the UCLA Medical Institutional Review Board. Participants received \$15/h for participating.

Nineteen younger adults were used as a comparison group. They met similar inclusion requirements as the older adult sample. This sample included 10 women and 9 men (mean age = 21.8 years, $SD = 3.7$). Behavioral and fMRI data from both groups and DTI data from the younger adult sample have been previously reported (Cohen

et al., 2014, 2016; Reggente et al., 2018), but the DTI analyses with older adults are reported here for the first time.

1.2. Design and task stimuli

On each study trial, participants were presented with an individual to-be-learned word that was preceded by a value cue denoting the number of points they would earn for later recalling that item. Their goal was to study the items such that they maximized their score on a free recall test that immediately followed each list's encoding. Each item was worth either a low (1, 2, 3) or high (10, 11, 12) value, with point-values chosen to produce the largest differences between low- and high-value items. Participants learned seven lists of words, with the first two lists considered as practice lists. Each list consisted of 24 unique words, with an equal number of items randomly assigned into each of the six possible point-values. The point-value associated with each word and list order were counter-balanced across participants. These word stimuli were 4–8 letter English nouns sampled from the [Toglia and Battig \(1978\)](#) word norms, clusters 6 and 7, and were rated as highly familiar (range: 5.5–7 on a 1–7 scale).

1.3. Procedures

Each participant completed the entire VDR memory task in the MRI scanner. Prior to scanning, participants were instructed about the memory task, and completed two practice lists with feedback. This extensive practice session was administered because selectivity is typically stronger on the third and subsequent lists ([Ariel and Castel, 2014](#); [Castel, 2008](#); [McGillivray and Castel, 2011](#)), as participants establish their learning strategy. During a study trial, participants viewed a value-cue for 2 s, saw a fixation cross jittered for 3–6.75 s, and then saw the word for 3.5 s ([Fig. 1](#)). The value-cue was presented on a background designed to look like a gold coin. Afterwards, they saw a fixation cross for 1.5 s, and then completed a basic vowel-consonant judgment task for 3.75–8.75 s. In the vowel-consonant judgment task, 2 letters (50% of trials), 4 letters (25% of trials), or 6 letters (25% of trials) were presented sequentially in a pseudorandom order, with an approximately equal number of vowels and consonants presented. Each letter was shown for 1 s, followed by a 0.25 s fixation between letters. A 1.5 s blank screen was presented after the final letter. Each list began with 10 s of fixation, and ended with 15 s of the vowel-consonant task. Approximately 10–20 s after the end of each list, the participant was given 90 s to recall as many studied items as possible from the previous list. After each recall test, the participant was given feedback on the number of points earned on that list. This procedure was repeated across the two practice lists and five test lists.

1.4. Scanning procedure

MRI data were acquired with a 3.0T Siemens Tim Trio Scanner at the UCLA Staglin IMHRO Center for Cognitive Neuroscience using a 12-channel receive-only phased array head coil. High resolution T1-weighted anatomical images were obtained using a 3D MPRAGE sequence with GRAPPA acceleration (TR = 1900 ms, TE = 3.26 ms, flip angle = 9°, FoV = 250 mm, 176 slices, voxel

size = 0.98 × 0.98 × 1.0 mm). Diffusion weighted imaging data were obtained using a multi-directional weighted spin-echo echoplanar imaging (EPI) sequence (TR = 9000 ms, TE = 93 ms, 64 non-collinear directions, b-value = 1000 s/mm², echo spacing = 0.69 ms, FoV = 190 mm, 60 axial slices, voxel size = 2.0 × 2.0 × 2.0 mm) with a non-diffusion weighted reference volume (b-value = 0 s/mm²). Prior to acquiring these structural scans, functional EPI data were obtained; findings from analysis of the functional data have been previously reported ([Cohen et al., 2014, 2016](#)). Head movement was minimized by inserting extra cushions between the participant's head and the coil. Stimuli were presented using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA), and images were shown with either a custom-built MR-compatible rear projection system or MR-compatible goggles (Resonance Technology, Inc.).

1.5. Diffusion tensor imaging data processing

Older adult DTI data were processed using the same procedure described for the young adult dataset by [Reggente et al. \(2018\)](#). Briefly, diffusion weighted images (DWIs) were preprocessed using the FMRIB's Diffusion Toolbox (FMRIB Software Library, FSL version 5.0.9; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL>). First, all DWIs were corrected for eddy currents and motion using `eddy_correct` and aligned to the b0 reference volume. Second, the Brain Extraction Tool (BET) was used to generate brain-tissue-only masks for each subject that were applied to all diffusion images ([Smith, 2002](#)). Next, tensor models were fit to the diffusion data from each voxel to create subject-specific whole-brain maps of mean diffusivity (MD), a measure of how easily water flows across each of the principle directions of the tensor—where higher MD indicates less directional specificity in water flow. This measure is sensitive to structural white matter damage and differences in axon density and diameter ([Beaulieu, 2002](#)), and is a particularly effective predictor of age-related memory impairment ([Charlton et al., 2010](#)). Additionally, compared with fractional anisotropy (FA), MD has been shown to be a more sensitive marker of age-related memory disorders including Alzheimer's disease and mild cognitive impairment ([Acosta-Cabrero et al., 2010](#); [Bosch et al., 2012](#); [Salat et al., 2010](#); [Sexton et al., 2010](#)). Moreover, FA is less likely to capture differences that occur when diffusivity is affected in multiple directions simultaneously, as is the case with age-associated demyelination ([Bosch et al., 2012](#); [Sexton et al., 2010](#)). Because high MD values imply weaker structural integrity, we predicted that high MD values in tracts relevant to verbal learning would be associated with worse memory, particularly for valuable items due to these tracts being less able to support efficient processing.

Finally, FSL's BEDPOSTX was used to create an estimation of diffusion parameters at each voxel. This procedure uses a Markov-chain Monte Carlo sampling technique that accounts for crossing fibers to generate a Bayesian estimation of diffusion parameters at each voxel in a diffusion image ([Behrens et al., 2003, 2007](#)). We leveraged this metric given that tract strength measures developed through DTI tractography have been shown to correlate strongly with anatomical connectivity determined using retrograde tracer injections ([Donahue et al., 2016](#)).

All analyses were computed in subject-specific diffusion space. Regions of interest (ROIs) used for calculating mean MD were initially

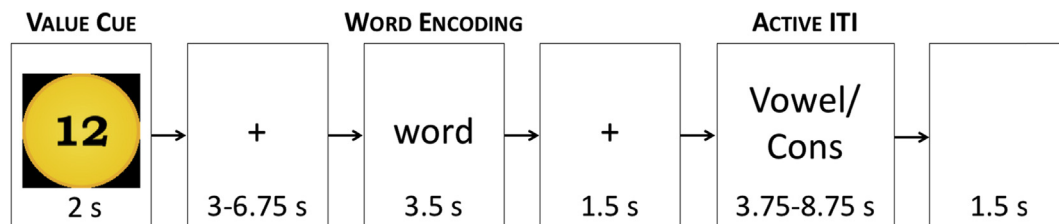


Fig. 1. Encoding task schematic.

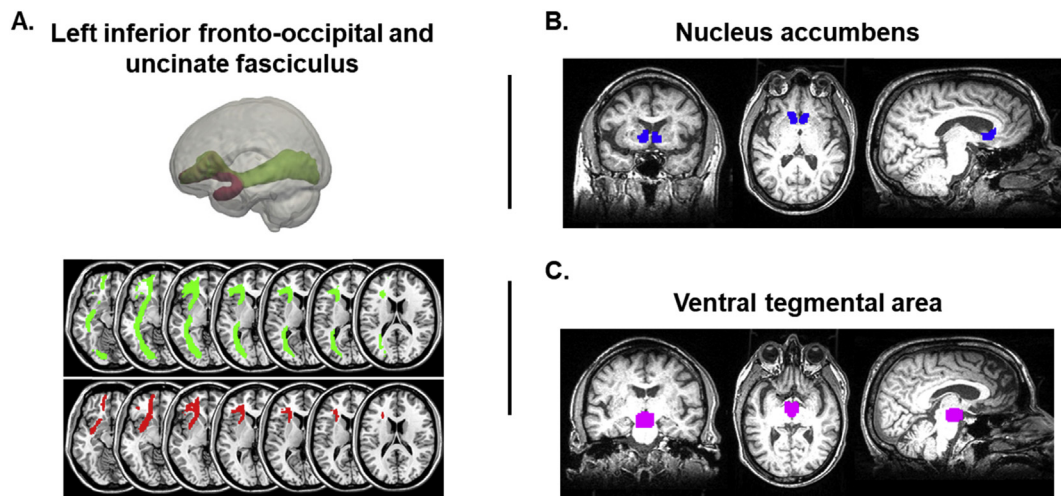


Fig. 2. Regions of interest: **A)** Left inferior fronto-occipital fasciculus (green) and uncinate fasciculus (red) overlaid on a standard T1-weighted template in MNI space. Masks were defined using a probabilistic white matter tractography atlas (Mori et al., 2005). **B)** Nucleus accumbens (NAcc) ROI, aligned to and overlaid on a representative subject's MPRAGE. The NAcc was defined using FreeSurfer's automatic subcortical segmentation routine. **C)** Ventral tegmental area (VTA) ROI, aligned to and overlaid on a representative subject's MPRAGE. The VTA was defined using a probabilistic atlas of the human VTA (Murty et al., 2014).

mapped in Montreal Neurological Institute (MNI) space. These ROIs were first registered onto each subject's structural space (MPRAGE) using 12-parameter linear-affine registration using FMRIB's Linear Image Registration Tool (FLIRT). Next, FLIRT was used to bring these ROIs into subject-specific diffusion space using the non-diffusion-weighted b0 reference volume. Each subject-specific ROI registered in diffusion space was also examined visually and no major anatomical deviations were observed.

Our primary ROIs of interest—left IFOF and left UF—were defined based on the John Hopkins University (JHU) white matter tractography atlas (Hua et al., 2008; <http://cmrm.med.jhmi.edu>; Fig. 2). Since IFOF and UF have substantial anatomical overlap, we decided to exclude all UF voxels from the IFOF masks and only analyze those portions that do not show overlap with UF (Reggente et al., 2018). As a control analysis designed to rule out the possibility that generalized differences in white matter integrity correlated with our behavioral measures, we examined a left corticospinal tract ROI defined from the JHU atlas. For all JHU atlas ROIs, we applied a 10% probability threshold to ensure sufficient coverage of each pathway, while avoiding excessive sparsity/shrinkage that would result if higher thresholds were applied (Reggente et al., 2018). Results from the right hemisphere IFOF, UF, and corticospinal tract are reported as supplemental data (Supplemental Table 4).

To analyze structural connectivity between NAcc and VTA, we used the diffusion estimation generated by BEDPOSTX and FSL's PROBTRACKX to create a subject-specific metric of seed to target ROI connectedness (Behrens et al., 2003). This procedure was carried out since no atlas for this pathway was publicly available and because we wanted to investigate whether a previously-observed relationship between connectivity strength and high-value recall in younger adults (Reggente et al., 2018) would also be found in older adults. First, FreeSurfer's subcortical segmentation routine was used on each subject's MPRAGE scan to generate left and right NAcc ROIs. As the VTA is challenging to appropriately demarcate in T1-weighted MR images of individual subjects, a VTA ROI was defined for each subject using a probabilistic atlas of human VTA (Murty et al., 2014; <http://web.duke.edu/adcocklab>) with a 50% probability threshold. The pathway from each NAcc ROI to the VTA was calculated using 5000 samplings of the distribution of diffusion parameters from each voxel within the seed ROI; the distribution of streamlines was used to estimate a likely tract location.

Our measure of interest was the total number of samples from the seed ROI that reached the target mask. To control for variance in ROI size (due to either subject-specific registration and FreeSurfer

segmentation differences), we divided the total streamline count by the number of samples sent from the seed mask (i.e., 5000 * number of voxels in the seed ROI) (Johansen-Berg et al., 2005). Partial correlations, controlling for the size of the subject-specific target ROI, were computed between this tract strength value and memory measures of interest.

1.6. Data analysis

Statistical analyses were conducted using SPSS 22.0 (SPSS, Inc., Chicago, IL). Pearson correlation coefficients were computed between MD values for our tracts of interest and our primary measures of memory performance: number of high-value items recalled, number of low-value items recalled, and a measure known as the *selectivity index* (Castel et al., 2002; SI), with 95% confidence intervals reported in brackets. The SI reflects how selective a participant was in preferentially learning and retrieving valuable items and is computed using the formula: (actual score – chance score)/(ideal score – chance score). A participant's achieved score is compared with the highest score they could have achieved given the number of items they retrieved (ideal score) and compared with chance performance (i.e., mean point-value multiplied by the number of words recalled). Each subject's SI was an average across all 5 lists presented in the MRI scanner, with the contribution of each list weighted by the number of items recalled. Within age-group correlations between high-value item recall, low-value item recall, and SI with DTI data for our three primary tracts (left IFOF MD, left UF MD, and NAcc-VTA connectivity strength) were controlled for multiple comparisons using a sequential Holm-Bonferroni method (Holm, 1979; total tests = 9). In this method, observed *p*-values for all primary analyses within each age group are ranked lowest to highest, with the minimum adjusted alpha corresponding to a full Bonferroni correction—for this study, $\alpha = .05/9 = 0.0056$. If the lowest *p*-value meets that threshold, the next-lowest is compared to $\alpha = .05/8 = 0.00625$, and so on. To compare the strength of the relationship between a given region's MD and high-value and low-value item recall, a two-tailed test for the difference between two dependent correlations was used (Steiger, 1980, <https://quantpsy.org/corrtest/corrtest2.htm>).

Table 1
Demographics and recall performance.

	Younger Adults	Older Adults	t-statistic (df = 40)
Total Recall	11.83 (3.90)	7.63 (4.01)	3.42; $p = .001$
Low-Value Recall	3.18 (2.72)	1.99 (2.20)	1.57; $p = .125$
High-Value Recall	8.65 (1.87)	5.64 (2.79)	4.02; $p < .001$
Selectivity Index	.61 (.22)	.47 (.35)	1.51; $p = .140$

Note. Standard deviation in parentheses.

2. Results

2.1. Behavioral performance

Younger adults recalled significantly more items than older adults (Table 1). More specifically, younger adults recalled significantly more high-value items, though they did not significantly differ from older adults in recall of low-value items (for detailed behavioral results reporting, see Cohen et al., 2016). Nevertheless, strong value effects on memory were observed in both groups as the average selectivity index was significantly above 0 (i.e., with 0 representing value-insensitive recall) for both younger adults, $t(18) = 11.93, p < .001, d = 2.74, [1.74, 3.73]$ and older adults, $t(22) = 6.52, p < .001, d = 1.36, [0.78, 1.92]$.

2.2. Memory performance and white matter microstructure

Compared with the young adult sample, older adults showed significantly higher MD values in left IFOF (with UF voxels masked out) and UF, suggesting that the integrity of these tracts was reduced with age (Table 2). To determine how these changes in MD may have influenced value-related selectivity, we first examined correlations between structural integrity (lower MD) and recall performance in these tracts. For older adults, lower MD in IFOF was significantly associated with increased recall of high-value items, but not low-value items (Table 3, Fig. 3). The difference in correlation magnitude between high-value and low-value items showed a marginal trend, $z = 1.92, p = .055$. When controlling for age within the older adult sample, the semi-partial correlation between left IFOF MD and high-value recall still showed a strong trend ($r = -0.37, p = .051, [-0.68, 0.05]$). For young adults, MD of the IFOF was not significantly correlated with recall of either item type (all p 's > 0.396). Analyses using the full IFOF mask, without the UF exclusion, show similar results (Supplemental Table 4).

The observed relationship between memory for high-value items and MD of the left IFOF in older adults survived controlling for multiple comparisons. Because we observed an outlier with MD over 2 standard deviations above the mean for the IFOF ROI, and almost 2 SD below the mean on high-value recall, we also examined these associations using Spearman's rank correlation coefficient. Unlike the Pearson correlation, this non-parametric measure is highly robust to the effects of outliers (Croux and Dehon, 2010). A significant relationship between high-value recall and MD was still observed in left IFOF ($\rho = -.56, p = .006$). Thus, this finding in IFOF does not appear to be due to the

Table 2
Tract-specific measures of mean diffusivity.

	Younger Adults	Older Adults	t-statistic (df = 40)
IFOF, left	0.83 (0.03)	1.02 (0.14)	5.64; $p < .001$
IFOF, right	0.84 (0.03)	1.00 (0.10)	6.75; $p < .001$
UF, left	0.86 (0.06)	1.00 (0.10)	5.25; $p < .001$
UF, right	0.93 (0.06)	1.10 (0.11)	6.12; $p < .001$

Note. Mean diffusivity ($\times 10^{-3} \text{ mm}^2/\text{s}$). Standard deviation in parentheses. IFOF = inferior fronto-occipital fasciculus (UF voxels excluded); UF = uncinate fasciculus.

Table 3

Pearson correlations between recall measures and mean diffusivity in left hemisphere tracts of interest, and connectivity strength in NAcc-VTA, for younger and older adults.

	IFOF		UF		NAcc-VTA	
	r	p	r	p	r	p
Younger adults						
High-value	-.19	.430	-.64	.003	.51	.013
Low-value	-.21	.396	-.07	.775	-.17	.493
SI	.24	.332	-.32	.176	.53	.020
Older adults						
High-value	-.56	.005	-.12	.572	.10	.660
Low-value	-.12	.602	.20	.361	.04	.867
SI	-.26	.230	-.32	.141	.02	.934

Note. SI = selectivity index; IFOF = inferior fronto-occipital fasciculus (excluding voxels in UF mask); UF = uncinate fasciculus; NAcc-VTA = connectivity strength between nucleus accumbens and ventral tegmental area (controlling for VTA ROI size). Correlations that reached significance level controlled for multiple comparisons using the Holm-Bonferroni procedure are highlighted in bold.

influence of outliers.

Next, correlations between MD in the left UF with recall were examined in each age group. As Reggente et al. (2018) reported using FA as a measure of white matter integrity, here we found that MD in left UF was correlated with recall of high-value items in younger adults (note that Reggente et al. (2018) reported a positive correlation, since higher FA values are indicative of more robust white matter structure, whereas we observed a negative correlation, as lower MD values are indicative of more robust white matter structure). Mean diffusivity is a particularly sensitive measure for age-related changes in white matter structural integrity (Bosch et al., 2012; Sexton et al., 2010) and an effective predictor of individual differences in memory (Charlton et al., 2010). However, we observe no such correlation in either hemisphere in older adults (Table 3; Supplemental Table 4). For younger adults, the difference in correlation magnitude between high and low-value items was significant for left UF, $z = 2.52, p = .012$. As a control analysis, MD of the corticospinal tract was examined. MD was not significantly correlated with high-value recall or low-value recall in either age group, all $|r| < 0.24, \text{ all } p > .1$ (Supplemental Table 4). Selectivity index was not significantly associated with MD in any of the above tracts, all $|r| < 0.32, \text{ all } p > .1$. Hierarchical regression models examining whether the relationship between each tract's MD and high-value item recall differed in magnitude between the age groups were not significant, likely due to limited statistical power to detect between-subjects interactions (Supplemental Table 1).

2.3. Memory performance and reward circuit tract strength

Lastly, contributions of the NAcc-VTA reward circuit to VDR were examined. Similar to Reggente et al. (2018), we combined the left and right NAcc ROIs into a single bilateral NAcc mask and assessed the relationship between the mean NAcc-VTA tract strength with our recall measures. Partial correlations are reported controlling for the size of the VTA target ROI. Mean tract strength did not significantly differ between older adults ($M = .015, SD = 0.018$) and younger adults ($M = 0.014, SD = 0.014$), $t(40) = 0.26, p = .797, d = 0.08, [-0.53, 0.69]$. For younger adults, NAcc-VTA tract strength was significantly associated with recall of high-value items ($r = 0.51, p = .013, [0.07, 0.78]$), but not low-value items ($r = -0.17, p = .493, [-0.58, 0.31]$), and this difference in correlation magnitude was significant, $z = 2.78, p = .005$. NAcc-VTA tract strength did not significantly correlate with memory for either high-value ($r = 0.10, p = .660, [-0.33, 0.49]$) or low-value ($r = 0.04, p = .867, [-0.38, 0.44]$) in older adults. To determine if this null effect in older adults was due to small sample size, we conducted a post-hoc power analysis using GPower (version 3.0; Heinrich Heine

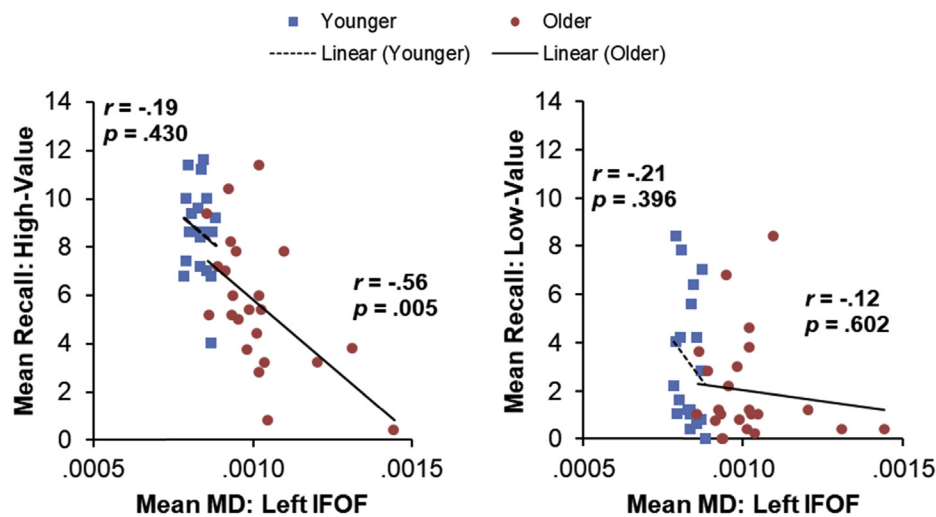


Fig. 3. Recall of high-value and low-value items by mean diffusivity in left IFOF. Correlation statistics presented for younger adults (left) and older adults (right). MD = mean diffusivity; IFOF = inferior fronto-occipital fasciculus.

Universität Düsseldorf; <http://www.gpower.hhu.de/en.html>) with the effect size observed in younger adults ($r = 0.51$). This study had an estimated power of .73 to observe a comparable significant relationship between NAcc-VTA tract strength and valuable item recall in older adults.

3. Discussion

In the current study, diffusion tensor imaging was used to determine whether individual differences in the microstructural integrity of white matter tracts in older adults is related to their ability to selectively encode and retrieve valuable information. Most notably, higher white matter integrity (lower MD) in the left IFOF was associated with increased memory for valuable items in older adults. In contrast to the findings from the younger adult sample who completed the same task (Reggente et al., 2018), we did not find a relationship between memory performance and white matter integrity in left UF for older adults, nor did the older adult sample show a significant relationship between NAcc-VTA tract strength and memory for valuable items. These findings are discussed in detail below.

The IFOF is part of a semantic processing network (Binder and Desai, 2011) that connects frontal regions involved in goal-directed learning and retrieval search (Dobbins and Wagner, 2005; Skinner and Fernandes, 2007) with temporal and occipital cortices involved in semantic and visual processing (Catani and Thiebautdeschotten, 2008; Duffau et al., 2013). In line with our predictions, MD in left IFOF was significantly inversely related to older adults' memory for high-value items but not low-value items, suggesting that the structural integrity of the IFOF is related to the encoding of high-value items. Older adults also showed significantly higher MD in the IFOF relative to younger adults, suggesting the presence of moderate age-related white matter atrophy. The relationship between MD in left IFOF and memory for valuable items remained a very strong trend when age was controlled. However, because the correlation magnitude was somewhat reduced when age was included in the model, it seems likely that in older adults both longstanding individual differences in IFOF integrity and age-related changes in this tract affect selective learning. Effects of age-related changes in IFOF should be examined in future longitudinal research. For the younger adult sample, MD in the IFOF was not correlated with these measures of recall.

In the VDR task, more items are presented than participants can remember; to optimize their performance, they must selectively encode only the most valuable items. The agenda-based regulation framework posits that time, resources, and effort are allocated based on a goal-

oriented agenda that aims to maximize performance (Ariel et al., 2009; Dunlosky and Ariel, 2011; Middlebrooks et al., 2017). In accordance with this framework, both older and younger adults typically report selectively using elaborative semantic encoding strategies when learning valuable items (Ariel et al., 2015; Cohen et al., 2017). In the present dataset, 16 of 23 older adults and 14 of 19 young adults reported using strategies related to the meanings of the words to support encoding (see the supplemental material of Cohen et al., 2016, for a full description of these self-report data). Thus, we interpret the current findings to suggest that, particularly in older adults, integrity of the IFOF may account for significant variance in this enhanced semantic processing of valuable items. Functional MRI data from this same set of subjects showed that older adults had increased activity in left VLPFC, left lateral temporal cortex, and bilateral occipital cortex during encoding of valuable words (Cohen et al., 2016). Based on its anatomical location (Catani and Thiebautdeschotten, 2008), the IFOF is a prime candidate for coordinating these regions during VDR.

Interestingly, unlike what Reggente et al. (2018) reported in young adults, selectivity index for older adults was not reliably correlated with any of our white matter measures (Table 3); we only observed a correlation between high-value item recall and white matter integrity in IFOF. While high-value item recall is often related to selectivity, the selectivity index measure is also highly dependent on one's ability to inhibit encoding of low-value items. For example, remembering two of the highest value items and zero low-value items would be considered poor high-value memory performance but perfect value selectivity. Cohen et al. (2016) reported that selectivity in older adults appeared to be driven to a large extent by reduced attention to low-value items. Because structural integrity in the left IFOF is likely to be associated with the efficient use of active encoding strategies, it makes sense that MD values in this tract in older adults correlate with successful encoding of high-value items, rather than with selectivity index.

A second key finding was that tract strength in the NAcc-VTA reward circuit, measured via probabilistic tractography, was not correlated with memory for valuable items in older adults. Additionally, older adults did not significantly differ from younger adults on NAcc-VTA tract strength. This neural pathway is activated in response to anticipated rewards (Adcock et al., 2006) and modulates the encoding of information into long-term memory via its dopaminergic inputs to the hippocampus (Bethus et al., 2010; Lisman and Grace, 2005; Rossato et al., 2009). Younger adults in this experiment did show a significant relationship between higher NAcc-VTA tract strength and improved memory for valuable items (Reggente et al., 2018). One plausible reason why this relationship was not significant in older adults is that

normal aging is associated with a substantial decline in the amount of striatal dopamine transporters and receptors (Kaasinen and Rinne, 2002; Karrer et al., 2017). More specifically, aging is associated with reduced amounts of D₁ and D₂ receptors (Düzel et al., 2010; Rinne et al., 1990; Wang et al., 1998), with loss of both receptor types estimated to be between 2% and 5% a decade (Rinne et al., 1990; Seeman et al., 1987). During probabilistic reward learning, neural correlates of reward prediction error are reduced in older adults (Samanez-Larkin et al., 2014), and these impairments are mitigated by administration of L-dopa, a dopamine agonist (Chowdhury et al., 2013). Thus, declines in the availability of dopamine may limit the extent to which activation in reward circuitry supports value-driven encoding and recall in older adults. Although we did not observe age-related differences in the structural integrity of the NAcc-VTA tract, functional differences in this tract may have caused older adults to rely on different neural ensembles to successfully perform the task.

Finally, the integrity of white matter in left UF did not correlate with memory performance in older adults, in contrast to what Reggente et al. (2018) observed in younger adults. In prior research, UF integrity has been associated with reward sensitivity (e.g., Camara et al., 2010; Bjornebekk et al., 2012), verbal episodic memory (Niogi et al., 2008), processing of semantic information (de Zubicaray et al., 2011), and with interactions between these systems (Von Der Heide et al., 2013). Reggente et al. concluded that the correlation between UF integrity and recall of high-value information in the VDR task was likely due to UF having a role in control of semantic information processing. This attribution was based in part on their observation that NAcc-VTA tract strength correlated with selectivity index, a measure of reward sensitivity in this task, while UF FA values showed no such correlation. It is possible that, although individuals in both age groups appear to modulate semantic processing as a function of item value, there are still subtle but important differences in how they do so. Cohen et al. (2016) found that young adults who increase activity in the semantic brain network for high-value items show improved value-related selectivity, whereas older adults who decrease activity for low-value items show improved value-related selectivity. This distinction may hold explanatory value for the present findings.

A possible explanation for the divergent findings across age groups is that, in younger adults, the correlation between UF integrity and high-value recall reflects the ability to integrate cue information signaling a high reward value with the semantic knowledge that enhances encoding of high-value words (Von Der Heide et al., 2013). In other words, young adults with stronger UF connectivity may be more motivated and/or better able to implement semantic encoding strategies for high-value items. In contrast, in older adults, semantic processing seems to occur independently of activity in the dopaminergic reward system; the reward system is not selectively activated on high-value items, and memory selectivity seems to be mediated by a strategy-driven reduction in semantic encoding when learning low-value items, not by enhanced motivation to learn high-value items (Cohen et al., 2016). Thus, it is plausible that in older adults, individual differences in the ability to successfully engage semantic encoding processes on high-value words would rely on white matter fiber connections that are less strongly associated with processing emotional/reward valence. That would explain the current finding that structural integrity of the IFOF, and not the NAcc-VTA pathway, was associated with memory for high-value words in older adults. Consistent with this suggestion, recent work has proposed that the IFOF is the primary tract responsible for processing of semantic information, with the UF typically playing a more supplementary role (Duffau et al., 2013; Nugiel et al., 2016).

One limitation of the current study was the relatively small older adult sample size (although this sample size is comparable to other fMRI and DTI studies with older adult samples, see Geddes et al., 2018). Notwithstanding, our main finding in IFOF was both large in magnitude and survived controlling for multiple comparisons. However, because our findings regarding the NAcc-VTA reward pathway were based on a

null effect, this analysis in particular should be replicated in future research to rule out the possibility of a false negative. That said, the lack of a relationship between the NAcc-VTA pathway integrity and VDR performance parallels the lack of BOLD signal activation in this system in older adults in the VDR task (Cohen et al., 2016). The small sample size also means that the lack of correlation with VDR performance and MD in the UF should also be interpreted cautiously. Additionally, direct comparisons of the findings in IFOF, UF, and NAcc-VTA between the two age groups were not significant, partially because this study focused on individual differences within age groups and was underpowered to detect significant differences in correlations between groups. Thus, future studies with larger samples will be needed to better characterize how the importance of different fiber tracts to VDR may change across the lifespan.

Because older adults showed largely intact value-directed remembering, but no significant relationship between the structural integrity of the NAcc-VTA pathway and selective learning, it may also be the case that semantic processing strategies relying on IFOF help to compensate for the lack of reward responsiveness in older adults. Younger and older adults selectively use elaborative strategies when learning valuable items (Ariel et al., 2015) that promote semantic processing (Craig and Tulving, 1975; Richardson, 1998) and result in increased episodic binding (Hennessee et al., 2018). Additionally, when presented with a large amount of information, older adults often report ignoring low-value items (Ariel et al., 2015) or allocate substantially more study time to valuable items (Castel et al., 2013). This goal-directed allocation of attention may be particularly important for older adults. Considering that older adults show increased activation in occipital cortex when encoding high-value items (Cohen et al., 2016) and that microstructural integrity of IFOF was associated with memory for high-value items in the current study, it may be that differential use of elaborative strategies such as visual imagery accounts for some of the variance in memory for valuable items. Additional research is necessary to determine to what extent differences in strategy use may account for these findings.

4. Conclusions

This study provides novel evidence that greater microstructural white matter integrity in the IFOF is associated with increased value-selective encoding and retrieval in healthy older adults. Unlike younger adults, older adults did not show a significant relationship between either UF white matter integrity or tract strength in the NAcc-VTA reward circuit and memory for valuable items. The IFOF may be supporting a compensatory role of enhanced deep encoding during motivated learning in older adults.

Acknowledgments

This work was supported by the Scientific Research Network for Decision Neuroscience and Aging (SRNDNA), as a subaward under National Institutes of Health grant AG039350 (to B.J.K, M.S.C, J.R., & A.D.C.); the National Institute on Aging at the National Institutes of Health (grant F31 AG047048 to M.S.C., grant R01 AG044035 to A.D.C.); the National Science Foundation (grant BSC-0848246 to B.J.K.); the UCLA's Staglin Center for Cognitive Neuroscience (pilot funds awarded to B.J.K.); and a UCLA Academic Senate Faculty Research Grant to B.J.K.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuropsychologia.2019.04.003>.

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